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Weber and Noise Adaptation in the Retina of the Toad *Bufo marinus*

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ABSTRACT Responses to flashes and steps of light were recorded intracellularly from rods and horizontal cells, and extracellularly from ganglion cells, in toad eyecups which were either dark adapted or exposed to various levels of background light. The average background intensities needed to depress the dark-adapted flash sensitivity by half in the three cell types, determined under identical conditions, were 0.9 Rh^*s^{-1} (rods), 0.8 Rh^*s^{-1} (horizontal cells), and 0.17 Rh^*s^{-1} (ganglion cells), where Rh* denotes one isomerization per rod. Thus, there is a range (~0.7 log units) of weak backgrounds where the sensitivity (response amplitude/Rh*) of rods is not significantly affected, but where that of ganglion cells (1/threshold) is substantially reduced, which implies that the gain of the transmission from rods to the ganglion cell output is decreased. In this range, the ganglion cell threshold rises approximately as the square root of background intensity (i.e., in proportion to the quantal noise from the background), while the maintained rate of discharge stays constant. The threshold response of the cell will then signal light deviations (from a mean level) of constant statistical significance. We propose that this type of ganglion cell desensitization under dim backgrounds is due to a postreceptoral gain control driven by quantal fluctuations, and term it noise adaptation in contrast to the Weber adaptation (desensitization proportional to the mean background intensity) of rods, horizontal cells, and ganglion cells at higher background intensities.

INTRODUCTION

In this study we first describe how the responses of single rods, horizontal cells, and ganglion cells in the dark-adapted toad retina are affected by weak background illumination. Here, our objective was to obtain a quantitative picture of how the sensitivities of the different cell types are changed in a preparation that is as "physiological" as possible. All three cell types were studied in the eyecup under identical conditions, and often two were studied in the same eye. The importance of studying all cell types in the same kind of preparation is exemplified by our finding that the background adaptation of toad rods in eyecups is significantly different from that found by recording the photocurrent of single rods with suction pipettes (Baylor et

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al., 1980; Lamb et al., 1981). If we had relied on data from rods drawn into pipettes, we would have overestimated the differences between the adaptation of rods and that of more proximal neurons.

Our second objective was to elucidate the role of ganglion cells as units displaying light adaptation independent of receptor adaptation. In the skate, cat, and rat, it has been shown that ganglion cells are desensitized by background lights dimmer than those that desensitize rods (Sakmann and Filion, 1972; Green et al., 1975; Green and Powers, 1982). We find in the toad retina, too, a range of low background intensities that desensitize ganglion cells, but not rods. We propose that the difference is related to how the different cell types react to the quantal fluctuations imposed by the background. At background levels where individual rods do not yet receive enough quanta to desensitize, the desensitization of ganglion cells could act to protect the retinal output from being congested by spike responses to random quantal fluctuations. The ganglion cell operating range would thus be reserved for light changes exceeding a criterion statistical significance (signal-to-noise ratio).

METHODS

Preparation, Stimulation, and Recording

The preparation of the eyecup, light stimulation, estimation of isomerization rates, and methods for extracellular recording have been described by Copenhagen et al. (1987). The methods for intracellular recording from rods and horizontal cells and cell identification are described in Copenhagen et al. (1990). The temperature was kept at 20°C in all experiments.

All backgrounds were presented as large fields. Stimulus spots were large enough to cover the entire central summation area of any cell under study (except where separately noted). Observing this, they were still kept as small as possible especially for ganglion cells, to avoid excessive stimulation of the inhibitory surround. For rods and horizontal cells, the usual test spot diameter was 520 μm, while for ganglion cells it varied somewhat depending on the size of the receptive field center (typically 300–600 μm in diameter). The stimuli were delivered as brief flashes (13.5 or 67 ms) or ON steps (actually 4-s pulses) of light.

Sensitivity

By the symbol Rh* we denote one photoisomerization per rod. Accordingly, background intensity is given as Rh^*s^{-1}. We define the flash sensitivities of rods and horizontal cells as the amplitudes of flash-evoked responses per Rh* (in millivolts per Rh*) and the flash sensitivity of a ganglion cell as the reciprocal of the flash intensity needed for a threshold response (1/Rh*), in all cases referring to stimuli that cover the whole central summation area (receptive field center) of the cell type under study. The ganglion cell threshold was taken as the lowest intensity at which one or more spikes occurred within a fixed 2-s time window (starting at 0.5 and ending at 2.5 s) after stimulus onset in at least half of the trials. It is worth emphasizing that the threshold thus defined does not depend on the detectability (signal-to-noise ratio) of the response (see below). Thus, our definitions of sensitivity are equivalent to the gain of Shapley and Enroth-Cugell (1984).

The sensitivity to step stimuli is defined as response amplitude per Rh^*s^{-1}, or, for ganglion cells, the reciprocal of threshold intensity $[1/(Rh^*s^{-1})]$.

Integration Time

The time span within which isomerization signals interact is defined by the integration time

$$t_i = (1/a_{max}) \int f(t)\, dt \tag{1}$$

where $f(t)$ is the amplitude of the response at time t and a_{max} its peak amplitude (Baylor and Hodgkin, 1973; Baylor et al., 1974). From this, two different ways of experimentally determining t_i follow. Firstly, if S_S (in millivolts per Rh* s^{-1}) is the step sensitivity and S_f (in millivolts per Rh*) is the flash sensitivity (for flash durations much shorter than t_i), then

$$t_i = S_S/S_f \tag{2}$$

Secondly, if the response time course is well defined, the flash response may be graphically integrated (the area under the response measured). If A(mVs) is the value of that integral, then

$$t_i = A/a_{max} \tag{3}$$

Summation Area

The spatial summation of a cell is expressed as a representative circular summation area A_S (mm^2) within which all isomerization signals are linearly summed with equal weight ("top-hat" approximation). Alternatively, it can be expressed as the number of red rods within A_S (= A_S × 15,000 mm^{-2} for the toad retina). For a fuller account of these measures, the reader is referred to Donner and Grönholm (1984), Copenhagen et al. (1987, 1990) and Donner (1987).

The Signal-to-Noise Ratio

We consider not only response thresholds and criterion amplitudes of responses, but also their statistical significance, i.e., signal-to-noise ratios. We have found it particularly useful to consider in each case the maximally obtainable signal-to-noise ratio. We assume that it is limited by three kinds of statistically independent quantal fluctuations: (*a*) in the numbers of photoisomerizations induced by the stimulus, (*b*) in the numbers of photoisomerizations induced by the background light, and (*c*) in the numbers of isomerization-like "dark" events spontaneously occurring in the rods (see Hecht et al., 1942; Rose, 1942, 1948; de Vries, 1943; Barlow, 1956, 1964; Baylor et al., 1980; Reuter et al., 1986; Aho et al., 1987; Copenhagen et al., 1987, 1990; Donner, 1989). When a stimulus is given, the cell will sum isomerization events from all three sources: stimulus, background, and "dark" events. Let the mean numbers (summed over A_S and t_i) be E_S, E_B (E_B = 0 in darkness), and E_D, respectively. Then the ratio of the mean number of stimulus events, E_S, to the (Poisson) standard deviation of the total number of events, $(E_S + E_B + E_D)^{0.5}$, is a measure of the signal-to-noise ratio at the input to the visual system (here denoted SNR_{in}). This sets an upper limit to the signal-to-noise ratio of any physiological response to the stimulus E_S:

$$SNR_{in} = E_S/(E_S + E_B + E_D)^{0.5} \tag{4}$$

The corresponding intensities I_S, I_B, and I_D of a large-field step stimulus, the background light, and the dark light, respectively, are obtained by dividing the appropriate event numbers by $A_S t_i$, yielding the alternative formulation

$$SNR_{in} = (A_S t_i)^{0.5} \times I_S/(I_S + I_B + I_D)^{0.5} \tag{5}$$

Eq. 5 reduces to the well-known square root or Rose-deVries law $I_S \sim I_B^{0.5}$, provided that three

conditions prevail: (*a*) threshold responses have a constant signal-to-noise ratio that is equal to (or a fixed fraction of) SNR_{in}, (*b*) the background intensity is high enough, so that quantal fluctuations from I_B are the dominant noise source, and (*c*) spatio-temporal summation ($A_S T_i$) is constant.

Adaptation, Desensitization, and Change in Signal-to-Noise Ratio

It is clear from Eqs. 4 and 5 that a background light that is not significantly weaker than the "dark light" always degrades the detectability of a fixed stimulus: in the presence of the background, a stronger stimulus than before is needed for detection of constant reliability. When we record from a single visual cell, the decreased detectability of the stimulus is in principle always evident as a decreased signal-to-noise ratio of the physiological response, but this need not necessarily be associated with a decrease in the amplitude of the response (a desensitization). Instead, there may just be an increase in noise amplitude. When the term adaptation is used in this article, we are always referring to true desensitization, never to the fact that a larger response and hence a stronger stimulus than before is required to ensure a constant signal-to-noise ratio when the noise has increased. Particularly, by the novel term noise adaptation we refer to a physiological process whereby noise reduces the sensitivity of a cell, so that a stronger stimulus than before is needed to produce a response of criterion amplitude.

RESULTS

Desensitization of Rod and Horizontal Cell Responses by Dim Backgrounds

The background intensity needed to decrease the sensitivity of a cell by 50% is a convenient index of its susceptibility to desensitization. We determined this in 11 rods and 7 horizontal cells by finding the background that halved the amplitude of the responses, to dim flashes of fixed intensity. The dark-adapted eyecup was exposed to 13.5-ms flashes at 22-s intervals. The test intensity was adjusted to elicit 1.5–2 mV responses, and as soon as the response amplitudes were stable, a 500-nm background field was turned on for about 110 s (Fig. 1). This was repeated several times with slightly different background intensities. The precise amplitude-halving intensity was obtained by interpolation.

The sensitivity of horizontal cells to large-field stimuli was 4–10 times higher than that of rods (see Table I). Thus the test flashes used for horizontal cells could be correspondingly weaker (in Fig. 1: 0.31 Rh* for the horizontal cell vs. 1.52 Rh* for the rod). The amplitude-halving background intensities, however, were approximately the same for both cell types. For example, in Fig. 1 the rod and the horizontal cell are exposed to the same background (0.58 Rh^*s^{-1}), and in both cases the flash responses are approximately halved. Still, because of the much higher flash sensitivity of the horizontal cell, the amplitude of the background-induced hyperpolarization is about four times larger. The halving of response amplitude was typically associated with a 1–1.5-mV steady hyperpolarization in rods (cf. Fig. 3, below) and a 6-mV hyperpolarization in horizontal cells.

The mean amplitude-halving background intensity was 1.3 Rh^*s^{-1} for rods and 0.8 Rh^*s^{-1} for horizontal cells (Table I; the rod and horizontal cell presented in Fig. 1 are nos. 4 and 6, respectively, in this table). When the results are stated in terms of sensitivity-halving backgrounds, even this moderate difference virtually disappears.

While the horizontal cell recordings could be carried out within a fully linear part of the intensity-response [$R(\log I)$] curve, the 1.5-mV criterion is slightly outside the linear range of dark-adapted rods (cf. the $R(\log I)$ functions in Fig. 3 of Copenhagen et al., 1990). The halving of response amplitude in rods therefore implied a sensitivity reduction of almost 60%. Taking this nonlinearity into account, the mean sensitivity-halving background for the rods in Table I becomes 0.9 Rh^*s^{-1}, not significantly different from that of the horizontal cells.

In four rods we investigated the effect of these weak backgrounds on the complete $R(\log I)$ function. In full agreement with the results of Fain (1976) and Hemilä (1977) we found a very slight (<10%) reduction of the maximum amplitude. It is thus clear that the halving of rod sensitivity is due almost exclusively to a displace-

FIGURE 1. Recordings from a rod (top; No. 4 in Table I) and a horizontal cell (bottom; No. 6 in Table 1) in darkness and during a 110-s exposure to a weak background light (0.58 Rh^*s^{-1}, as indicated below the recordings). Both cells were stimulated at 22-s intervals with test flashes of constant intensities: 1.52 Rh* for the rod and 0.31 Rh* for the horizontal cell. The flashes were preceded by 2-mV calibration pulses seen as upward "spikes." The horizontal cell was nine times more sensitive than the rod, while its integration time was shorter by half. Because of that, the background produced a four to five times larger maintained hyperpolarization in the horizontal cell. Observe that the background caused both a decrease in response amplitude and an increase in random membrane fluctuations.

ment of the $R(\log I)$ function to the right on the log intensity axis, not to a compression of the voltage response range.

Decrease in the Integration Times of Rods and Horizontal Cells due to Dim Backgrounds

Adapting background lights can change not only the sensitivities of cells, but also their summation properties. The summation of stimulus and background photons is critical for the signal-to-noise ratio of responses (see Eq. 5). Whereas the summation areas A_S of retinal cells appear to be little affected by very low levels of background illumination, this is not the case for integration times (cf. Donner, 1987).

The integration times t_i of rods and horizontal cells were first determined in dark-

ness by the two different methods expressed in Eqs. 2 and 3. The results for the individual cells are given in Table I. The grand mean of the two sets of values was 1.9 s for both rods and horizontal cells at this temperature. We then studied, in the same sample of cells, how much t_i (according to Eq. 3) was reduced by a sensitivity-halving background. The determination was based on experiments of the type shown in Fig. 1. On average, t_i decreased by 22% (range, 6–28) in rods and by 27% (range, 11–41) in horizontal cells. The difference between rods and horizontal cells is not statistically significant.

TABLE I

Response Characteristics of Red Rods and Rod-driven Horizontal Cells

Cell	Dark-adapted sensitivity	Background intensity halving response amplitude	Integration time		Mean of A and B
			Method A	Method B	
	*mV/Rh**	*Rh* s*$^{-1}$	*s*	*s*	*s*
Rods					
1	0.67	1.47	1.65	1.89	1.77
2	0.68	1.63	0.65	1.75	1.20
3	0.97	1.67	1.56	1.94	1.75
4	1.05	0.42	2.86	2.54	2.70
5	1.04	2.41	2.11	2.01	2.06
6	0.79	1.66	1.68	1.71	1.70
7	0.65	1.05	1.60	2.22	1.91
8	1.02	0.70	1.40	1.84	1.62
9	0.91	1.31	1.89	1.83	1.86
10	1.10	1.15	1.21	2.68	1.95
11	1.13	1.25	2.00	2.53	2.27
Mean	0.91	1.34 (0.91 after correction)	1.69	2.09	1.89
Horizontal cells					
1	4.12	1.34	1.34	2.14	1.74
2	5.39	1.26	0.83	1.95	1.39
3	8.19	0.25	3.30	2.33	2.82
4	9.94	0.34	2.53	2.42	2.48
5	6.14	0.82	1.94	1.57	1.76
6	9.25	0.85	1.16	1.42	1.29
7	2.25	0.87	1.93	1.74	1.84
Mean	6.47	0.82	1.86	1.94	1.90

Rod No. 4 and horizontal cell No. 4 were from the same preparation, as well as rod No. 11 and horizontal cell No. 7.

Buildup and Decay of the Background Effect in Rods

An analysis of 22 rod recordings of the type shown in Fig. 1 indicated that the response amplitudes to the same test intensity remained relatively constant during the time of the background exposure. Moreover, the first response after the termination of the background already regained the full dark-adapted amplitude. Thus the background-induced desensitization in rods builds up and decays within 15 s (cf. Hemilä, 1977; Greenblatt, 1983). In fact, it appears that the buildup phase is fin-

ished within just a couple of seconds, as is shown by the experiment illustrated in Fig. 2.

In Fig. 2, a sensitive rod (No. 8 in Table I) was exposed to 12-s periods of weak background light (0.73 Rh^*s^{-1}) alternating with 23-s periods of darkness. 3.5 s before each background period the retina was exposed to a 1.30-Rh* flash, and the same flash was repeated with varying delays after the background had been turned on. (In Fig. 2, the delays are 5 s in the top recording, 2 and 8 s in the bottom recording). It is seen that the response to a flash with 2 s delay was no larger than those obtained after longer delays. In the same series of recordings, the amplitudes of four responses to flashes with 3-s delays averaged 44% (range, 31–54) of the dark-adapted amplitude, and did not significantly differ from responses with longer delays. Thus, desensitization is nearly complete in 3 s.

It is interesting to note that, at the time the responses to flashes having 3-s delays peaked, the rods had received on average no more than three photoisomerizations

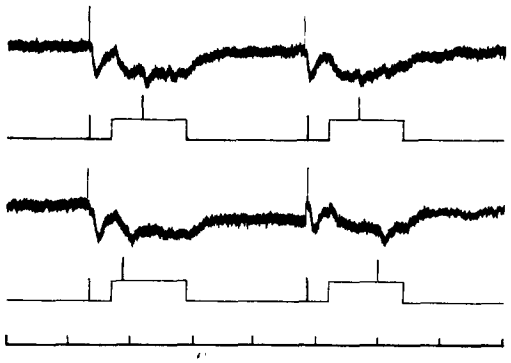

FIGURE 2. Recordings from a sensitive rod (No. 8 in Table I) exposed to 12-s periods of weak background light (0.73 Rh^*s^{-1}) alternating with 23-s periods of darkness, as indicated under the recordings. Also indicated are stimulus flashes (1.30 Rh*) presented 3.5 s before the background was turned on, and with varying delays after the background had been turned on (5 s delay in the top record, 2 and 8 s in the bottom record). The flashes were preceded by 2-mV calibration pulses seen as upward "spikes" in the recordings. The lowermost scale marks 10-s intervals.

from the background light. This implies that the desensitizing effect of a single photoisomerization must spread rapidly over a significant part of a dark-adapted rod (cf. Donner and Hemilä, 1978).

Rod Desensitization Bears No Strict Relation to Hyperpolarization

Inter-rod coupling allows extensive electrotonic spread of signals between rods at least in turtle and toad retinas (Schwartz, 1973; Fain, 1975; Copenhagen and Owen, 1976; Leeper et al., 1978). Conceivably, desensitization could also be conducted between rods via the network of interconnections. However, thorough studies in the turtle retina have indicated that a possible spread of desensitization must, at any rate, be much more limited than that of the light-induced signals (Copenhagen and Green, 1985).

We examined the possibility of inter-rod spread of desensitization in the toad retina by comparing the actions of three different background patterns centered on

the impaled rod: (*a*) a small-spot background (27 μm diam, only somewhat larger than the test spot); (*b*) an annular background (inner diam, 60 μm; outer diam, 110 μm); (*c*) a full-field background. Against each of these, a small (13 μm) stimulus spot was flashed on the impaled rod to test sensitivity.

Fig. 3 shows, for the full-field background, the type of data underlying the comparison. Relative sensitivities (ordinate) were plotted against the background-induced hyperpolarizations (abscissa) at several background intensities. (The intensity variable is thus eliminated from the plot.) The steady hyperpolarizations associated with a halving of response amplitude can be read directly from the plot (at log relative sensitivity = −0.3). The mean hyperpolarizations thus obtained for the different background configurations were (*a*) (small spot) 0.8 mV, (*b*) (annulus)

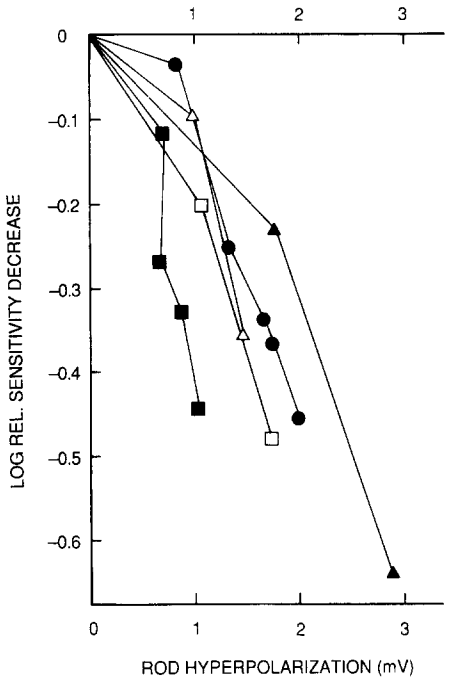

FIGURE 3. The log sensitivity decreases in rods induced by full-field backgrounds of different intensities, plotted as functions of the membrane hyperpolarization observed at each background intensity. Each symbol type refers to data from one rod. Log dark-adapted sensitivity is scaled to zero and corresponds to zero background-induced hyperpolarization for all cells (*upper left-hand corner*). 50% sensitivity depression is indicated by the log relative sensitivity −0.3. The saturating response in these rods was a hyperpolarization of 15–20 mV.

2.0 mV, and (*c*) (full-field) 1.3 mV. The conclusion is that there is no clear relation between desensitization and hyperpolarization. In fact, in view of the similarity to results from turtle retina (see above), it seems quite probable that the desensitization caused by the annular background was entirely due to light scattered onto the central rods.

Background-induced Noise and the Signal-to-Noise Ratio

Experiments of the type shown in Figs. 1 and 2 clearly demonstrate that background illumination reduces the signal-to-noise ratio of rod and horizontal cell responses in two ways: (*a*) the signal, i.e., the mean response amplitude, is reduced through desensitization; (*b*) the noise, i.e., the amplitude of random membrane potential

fluctuations in a low-frequency band (~0.1–1 Hz) is increased. A response-halving background typically increased the peak-to-peak low-frequency fluctuations in rods to 1–2 mV from 0.3–0.4 mV in darkness. Thus, a background that reduces the amplitude of the response to a given test flash by exactly 50% reduces the signal-to-noise ratio of that response by much more than 50%.

The fluctuations can be analyzed by Fourier techniques, as illustrated in Fig. 4 for one horizontal cell (No. 3 in Table I). (cf. also Reuter et al., 1986; Donner, 1989; for rods in the same species, see Baylor et al., 1980). *A* shows sample records, the top one taken in darkness and the bottom one in the presence of a dim steady background light (0.21 Rh^*s^{-1}), each including four flash responses. It is immediately evident that although the background reduces the amplitude of the responses by less than 50%, it makes them much more difficult to detect.

C shows the power spectra obtained by Fourier-transforming periods of "dark" and "background" records that did not include flash responses, and *D* (*plusses*) shows the difference spectrum of "background" minus "dark." The difference spectrum isolates the noise component added by the background light. In *D*, this added component is compared with two other spectra: (*squares*) the power spectrum of background records including flash responses (such as the lower sample in *A*), thus essentially catching the power of the flash responses; (*continuous line*) the spectral composition of a model flash response fitting responses recorded in the presence of the background (as shown in *B*). The good agreement of the difference spectrum with the two spectra that reflect the waveform of dim-flash responses indicates that the background-induced noise is built up of events having that waveform, i.e., of photoisomerization events.

It is possible to go further and calculate quantitatively the rate of such events needed to account for the power of the low-frequency voltage noise. Let the mean number of events that occur within the summation area within one integration time be X (the mean rate is then $X/A_S/t_i$). The standard deviation of these Poisson-distributed numbers is $\sqrt{X}$. If S is the sensitivity of the cell in terms of signal amplitude per isomerization within the receptive field (in millivolts per isomerization) and σ is the standard deviation (in millivolts) of the observed voltage fluctuations in the relevant frequency band, then

$$S\sqrt{X} = \sigma \tag{6}$$

The variance of the low-frequency noise (below 0.8 Hz) in the "background" spectrum of Fig. 4 *C* is $\sigma^2 = 0.034\ mV^2$, giving the standard deviation $\sigma = 0.184$ mV. The sensitivity of the cell in Fig. 4 under background illumination was 4.70 mV/Rh*, which, with a receptive field encompassing ~300 rods (cf. Copenhagen et al., 1990), corresponds to $S = 0.0157$ mV per isomerization in the receptive field. Eq. 6 then gives $X = 137$ isomerizations. On the other hand, since the background intensity was 0.21 Rh^*s^{-1} and the integration time $t_i \approx 2.1$ s in the presence of this background, a direct calculation indicates that the cell receives 132 isomerizations/$A_S t_i$ from the background. Thus we know, firstly, that a mean of 137 isomerizations will suffice to account for the electrical low-frequency noise, and secondly, that the background light in fact delivers a mean of 132 isomerizations. The conclusion then must be that the voltage noise is almost wholly due to the quantal fluctuations in the

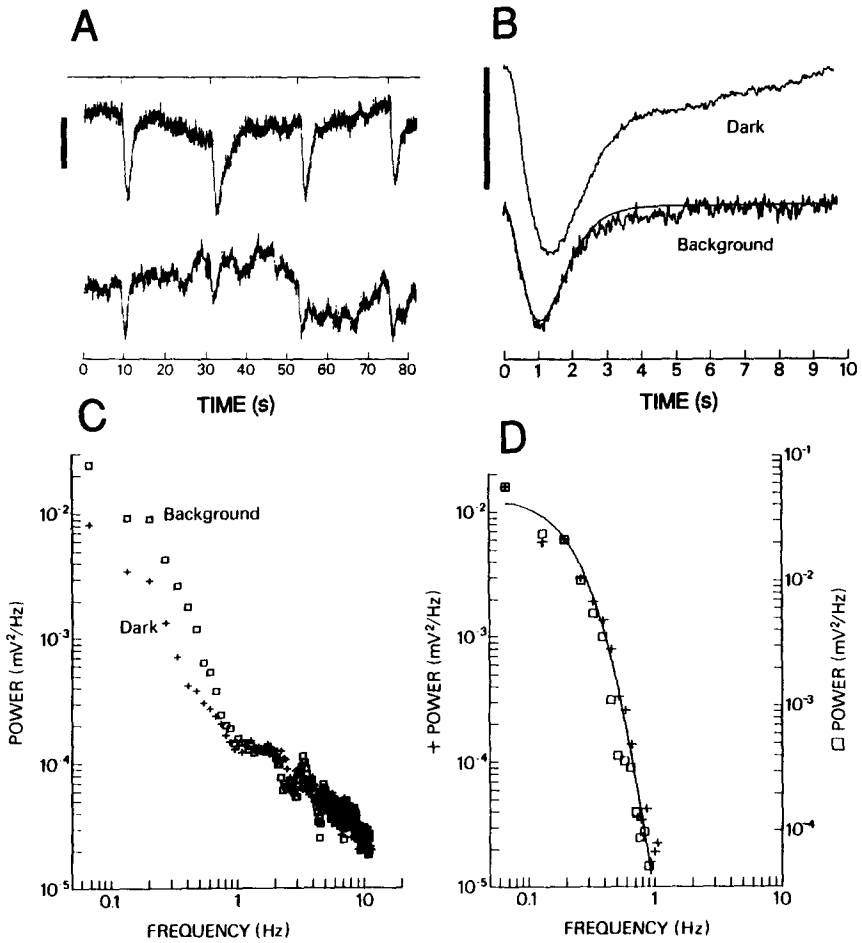

FIGURE 4. The membrane potential of a horizontal cell (No. 3 in Table I) in darkness and during background illumination. (*A*) Flashes of light (0.20 Rh*, 13.5 ms, 0.56 mm diam spot on the retina) were presented once every 22 s in darkness (*top*) and during background illumination (0.21 Rh^*s^{-1}, 1.5 mm diam; *bottom*). Vertical scale bar, 1 mV. The resting membrane potential and flash sensitivity in darkness were −40.5 mV and 8.19 mV/Rh*, respectively. The background light hyperpolarized the membrane by −4.2 mV and depressed sensitivity to 4.70 mV/Rh*. (*B*) Averaged light responses. Flash responses to 0.20 Rh* were averaged in darkness (10 responses, *top*) and during background (6 responses, *bottom*). Vertical scale bar, 1 mV. The smooth line superimposed on the bottom record is a model flash response, calculated according to the Poisson model of Baylor et al. (1974) (four stages, time constant = 361 ms). (*C*) Power spectra of membrane potential in darkness (*plusses*) and during background (*squares*). 1- or 2-min segments of membrane potential during continuous darkness and background (no flashes) were digitized (14.6 ms intervals), filtered (≤10 Hz), and Fourier analyzed by a 1024 FFT algorithm. The averages of six dark spectra and four background spectra are shown. Five point smoothing was applied to points above 1.2 Hz. The variances of the low-frequency component (calculated as the area under the power spectrum for frequencies ≤0.8 Hz) were σ^2 (background) = 0.034 mV^2 and σ^2(dark) = 0.017 mV^2. (*D*) The plusses show the difference spectrum (background-dark) of the spectra in *C;* the left ordinate refers to these data. The squares show the power spectrum of 15-s segments of recordings taken during background illumination and including flash responses (such as the lower record in *A*). The scale for this spectrum is shown on the right. The continuous line is the spectrum of a model response fitted to the average flash response during background illumination as shown in *B*.

background light. A similar calculation for the "dark" noise in this cell points to a mean rate of dark isomerizations = 0.027 Rh^*s^{-1}. This is in good agreement with the rate of spontaneous rod events obtained by Baylor et al. (1980) at the same temperature, 0.021 Rh^*s^{-1} as recorded from three-fourths of the length of the rod outer segment.

In summary, Fourier analysis of noise in rods (Baylor et al., 1980) and horizontal cells in toad suggests that the low-frequency noise, which degrades the detectability of dim-flash responses under weak background illumination, is mainly due to quantal fluctuations (cf. Reuter et al., 1986; Donner, 1989). Then Eq. 4 or 5 for SNR_{in} will give a fair description of how the signal-to-noise ratio of physiological responses is degraded by a background light. With very weak backgrounds ($\ll$ 0.8 Rh^*s^{-1}), the cells do not desensitize, and then the voltage noise will grow in direct proportion to the quantal fluctuations in the light.

Desensitization and Noise in Ganglion Cell Spike Discharges under Dim Backgrounds

Desensitization. The responses and maintained discharge of ganglion cells were studied extracellularly in eyecup preparations identical to those used for the intracellular rod and horizontal cell recordings described above. In a separate article we have given the absolute sensitivities, summation characteristics, and threshold-doubling background intensities of six thoroughly investigated, sensitive ganglion cells (cells Nos. 1–5 and No. 7 in Table I of Copenhagen et al., 1987). With stimulus spots covering the whole summation area of the receptive field center, the mean dark-adapted flash threshold of these six cells was 0.025 Rh* (range, 0.008–0.038 Rh*). The mean integration time of the threshold response was 1.76 s (range, 0.85–2.77 s), which is not significantly different from that of rods and horizontal cells. However, the mean background intensity needed to depress sensitivity by half (double threshold intensity) was only 0.17 Rh^*s^{-1} (range, 0.06–0.38 Rh^*s^{-1}), no more than 20% of the sensitivity-halving background of rods and horizontal cells. Thus ganglion cells are truly desensitized by backgrounds that do not affect the response amplitude of rods or horizontal cells.

No persistent noise increase. In rods and horizontal cells, the quantal noise of weak background lights was seen to be directly reflected as increased random fluctuations of the membrane potential, i.e., as "output" noise. The output noise of a ganglion cell lies in the randomness of its spiking. The very low rate of maintained activity in toad (often <1 spike/min) makes its randomness difficult to test rigorously. However, there is no evident regularity in the maintained discharge of healthy ganglion cells, except for the fact that spikes often occur in bursts of two to three within one second. Here we equate such a burst with a single spike and refer to both as one "event." The mean rate of such events can then be used as at least a semiquantitative measure of noise in the ganglion cell output (see Aho et al., 1987 on frog cells).

The maintained activity of ganglion cells was monitored in eight cells over different periods after the turning ON or OFF of dim backgrounds of various intensities. In seven of these cells, the discharge gradually stabilized at a constant low level, regardless of the intensity of the (dim) background. Only one of the cells was an

exception, in that the maintained discharge remained on an elevated level for the whole period of background illumination.

However, it took the cells a few minutes to regain the constant level of maintained discharge. This is illustrated in Fig. 5. When the background was turned on, the maintained firing rate transiently rose; correspondingly, it dropped transiently when the background was decreased. In either case, it returned to the original level over a period of 5–10 min. Sensitivity required a similar time to stabilize at a new level, while it will be recalled that rods reached their final sensitivity within a few seconds.

Thus, dim backgrounds that do not desensitize rods or horizontal cells, but only increase their membrane noise, have quite a different effect on ganglion cells. They are really desensitized, while their maintained rate of discharge remains constant instead. This suggests that the gain of the rod-to-ganglion cell transmission is reduced so as to keep the random spiking (output noise) constant in the face of

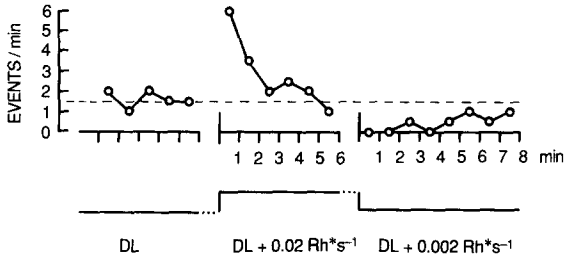

FIGURE 5. The maintained discharge of ganglion cells in darkness (DL, denoting dark light, *left*), after a dim background has been turned on (DL + 0.02 Rh^*s^{-1}, *middle*), and after the intensity of the background has been decreased (DL + 0.002 Rh^*s^{-1}, *right*). Each point gives the number of "events" (either one spike or a burst of two to three spikes, see text) during 1 min; mean values of recordings from two cells. (*Left*) Counts during each of 5 min preceding background onset. (*Middle*) Counts during each of 6 min starting 15 s after background onset, when the ON response had ceased. The 0.02 Rh^*s^{-1} background was on for a total of 15 min. (*Right*) Counts during each of 8 min starting 15 s after a 1-log-unit dimming of the previous background, when the OFF response had ceased.

increased random light fluctuations (input noise). If so, the desensitization must be proportional to the quantal fluctuations, i.e., to the square root of background intensity (Eq. 5). The increment threshold experiments described below confirm that this is the case.

Increment Threshold Functions of Rods, Horizontal Cells, and Ganglion Cells

Increment threshold functions were recorded in four rods, two horizontal cells, and five ganglion cells over 6 log unit ranges of background intensity. For the rods and horizontal cells, this implied finding, against each background, the stimulus intensity that would produce a response of criterion amplitude (2.8 mV). Each background was ON for 2–2.5 min, allowing four to five stimulus presentations at 30-s intervals. Even with stronger backgrounds it was clear that these periods were quite sufficient to ensure a steady state of adaptation. Background intensity was increased in 0.5- or 1-log-unit steps, and when the strongest one had been presented, the measurements against some of the backgrounds were repeated in reverse order. After the return to

a moderate background intensity, we could assess how much the cell's response to a fixed stimulus had decayed. Typically, the amplitude fell by half over a whole sequence of backgrounds lasting ~25 min. The recorded amplitudes were corrected for this decay by linear interpolation, and the exact intensity eliciting the (corrected) criterion amplitude 2.8 mV was determined by interpolation from the $R(\log I)$ curve. In the ganglion cells, the threshold intensity against each background was determined by 10–20 presentations of stimuli around threshold intensity. The interstimulus interval was 30 s and each background was ON for periods varying between 6 and 20 min.

Typical increment "threshold" curves from the three cell types are compared in Fig. 6. The intensities needed to produce a criterion response in the rod and horizontal cell are indicated by open circles and open squares, respectively. The threshold intensities of the ganglion cells are indicated by filled circles. The abscissa, common to all the cells, gives log background intensity (Rh^*s^{-1}). The ordinate gives threshold intensity for the ganglion cell. The rod and horizontal cell data have been vertically positioned for best coincidence with the ganglion cell data in the high-intensity range. This is done to facilitate comparison; it is permissible, because there is no *a priori* correspondence between ganglion cell thresholds and the amplitude criterion applied to the rod and horizontal cell.

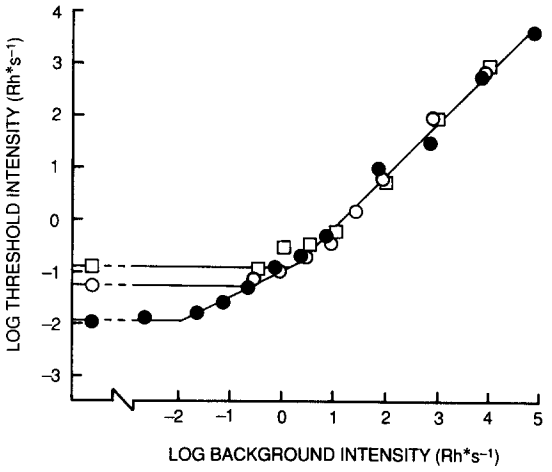

FIGURE 6. Increment thresholds of a ganglion cell (*filled circles*), a rod (*open circles*), and a horizontal cell (*squares*) as functions of log background intensity. For the two latter, "threshold" intensities were the intensities needed to produce a 2.8-mV criterion response. Step stimuli, full-field backgrounds. The abscissa (log background intensity) is common to all the cells. The ordinate, giving log threshold intensity, refers only to the ganglion cell. The rod data have been shifted downwards by 1.75 log units and the horizontal cell data by 0.8 log units to facilitate comparison between the three increment "threshold" curves by making the Weber ranges coincide. (Thus, in darkness the horizontal cell was in fact four times more sensitive than the rod.) The full-drawn curve is composed of straight segments with slopes 0, 0.5, and 1, illustrating background independence, square-root adaptation, and Weber adaptation, respectively.

Two main conclusions emerge from Fig. 6 and the other increment-threshold experiments. First, at high background intensities ganglion cells and rods, as well as horizontal cells, desensitize roughly in concert, approximating the Weber relation (slope 1). Secondly, in the range of very low background intensities that depress the sensitivity of ganglion cells, but not that of rods or horizontal cells, the former

desensitize along a slope of roughly 0.5, i.e., proportionally to the quantal fluctuations in the background.

In these experiments, we used ON-step stimulation. The purpose was to ensure that stimulus and background photons should be as equivalent as possible from the viewpoint of signal detection. (With a flash, all the stimulus photons are coincident in time, which may enhance their detectability.) The mean sensitivity-halving backgrounds in these experiments were 1.1 Rh^*s^{-1} for the rods, 0.9 Rh^*s^{-1} for the horizontal cells, and 0.06 Rh^*s^{-1} for the ganglion cells. Thus, the detection of step stimuli by the ganglion cell was indeed affected by even dimmer backgrounds than the detection of flash stimuli.

DISCUSSION

Background Adaptation in Rods

We find that rods start desensitizing at background intensities between 0.1 and 1 Rh^*s^{-1}, the average sensitivity-halving intensity being 0.9 Rh^*s^{-1}. From a functional viewpoint, it appears natural that a desensitizing mechanism should become operative only when each individual rod starts receiving isomerizations at a rate close to one per integration time (i.e., ~0.5 Rh^*s^{-1}). Dimmer backgrounds would leave the operating range of phototransduction essentially intact and pose no need for protecting it through desensitization. Nor could desensitization at lower background intensities serve to improve the signal-to-noise ratio at the rod output, because the background-induced membrane fluctuations and the light responses would be subject to the same amplitude reduction.

The background adaptation of rods in intact retinas and suction pipettes. The flash sensitivity of dark-adapted toad rods is approximately the same for microelectrode-penetrated rods in eyecups and single rods drawn into recording pipettes (1 Rh* evokes ~3–5% of the maximum response; Fain, 1975; Baylor et al., 1979*a*, *b*; Copenhagen et al., 1990). Yet there is a considerable discrepancy between the two preparations as regards the desensitization by weak backgrounds. In our eyecup preparation, sensitivity was halved by a background intensity of 0.9 Rh^*s^{-1}. Corresponding values for the photocurrent of isolated rods have been given as 7.7 Rh^*s^{-1} (Baylor et al., 1980) and 4–30 Rh^*s^{-1}, depending on the buffer used (Lamb et al., 1981). Earlier studies of rods in intact retinas of other species have yielded values that are even lower than ours: ~0.2 Rh^*s^{-1} in the eyecup of the snapping turtle (Copenhagen and Green, 1985) and 0.3–0.5 Rh^*s^{-1} in the perfused frog retina (Hemilä, 1977; Hemilä and Reuter, 1981).

It might be thought that the crucial difference between the preparations is the extent to which lateral interactions remain patent. However, experiments on the lateral spread of adaptation (see Results and Copenhagen and Green, 1985) gave no support to the idea that hyperpolarization, or some other rod-rod interaction, would be important for spreading desensitization. It must then be assumed that the experimental procedures for single-rod current recording change either (*a*) the magnitude of the desensitizing effect per photon absorbed, (*b*) its longitudinal spread within one rod outer segment, or (*c*) its rate of decay. Factor *c* cannot be crucial, since it fails to explain the dramatic effect of the very few isomerizations

collected during the first seconds of dim background illumination. The present evidence does not, however, allow a more precise identification of the decisive factor.

Distal and Proximal Adaptation in the Vertebrate Retina

Ganglion cells were found to be more susceptible than rods to desensitization by background light. This is in qualitative agreement with results from other species. In both the skate (Green et al., 1975) and the rat (Green and Powers, 1982) the difference in the background intensities that produce 1-log-unit desensitizations at the two levels was 2–2.5 log units. For rods and ganglion cells in the cat retina, the difference seems to be 2–4 log units (Steinberg, 1971; Sakmann and Filion, 1972; Shapley and Enroth-Cugell, 1984). Human a- vs. b-wave data (Faber, 1969) and a comparison of single macaque rods with human psychophysics (Baylor, 1987) suggest a difference of 3 log units in man.

All these differences are considerably larger than the mean difference we found with sensitivity-halving backgrounds in toad (0.7 log units with flash stimuli, 1 log unit with step stimuli). There is an interesting correlation between the number of rods per ganglion cell receptive field and the difference in rod and ganglion cell background adaptation. The rods in skate and mammals are much thinner than in toad, hence the receptive field of a large ganglion cell may comprise up to 200,000 rods in the cat (Leach et al., 1961; Enroth-Cugell and Shapley, 1973) compared with 4,000 in the toad. Thus, in the cat there is a wider gap than in the toad between the intensities where a ganglion cell receptive field and an individual rod, respectively, start collecting isomerizations at a significant rate.

Weber and Noise Adaptation

A compelling reason for retinal cells to adapt is the necessity to escape saturation, i.e., retain high differential sensitivity in the presence of sustained illumination (cf. Byzov and Kusnezova, 1971; Werblin, 1974). At higher background levels, toad rods, horizontal cells, and ganglion cells were all seen to desensitize in direct proportion to mean background intensity. Functionally, this realizes the Weber-Fechner law: the cells give constant responses to fixed contrast ratios over a wide range of illumination levels. At the same time it provides sufficient protection against saturation in DC-coupled cells like photoreceptors, which respond tonically to steady illumination.

At the lowest background intensities, toad ganglion cells did not show Weber adaptation, but desensitized approximately as the square root of background intensity. In a situation where the quantal fluctuations in the background constitute the dominant source of variability, a constant criterion response (e.g., one spike) will then signal light deviations (from the prevailing mean illumination level) of constant statistical significance. This is an essential aspect of what we shall refer to as "noise adaptation." It is noteworthy that, simultaneously, this type of desensitization will provide just sufficient protection against saturation (from background fluctuations) in AC-coupled cells, which respond to changes in illumination, but set up no tonic response proportional to the mean light level. This includes the most common types of anuran ganglion cells (Maturana et al., 1960; Ewert and Hock, 1972; Bäckström

and Reuter, 1975; Donner and Grönholm, 1984), and differentiation of the signal may be a ubiquitous feature of the transmission from receptors to ganglion cells in vertebrates (cf. Baylor and Fettiplace, 1977).

Possibly, all reported cases of "proximal" adaptation at low background intensities can be regarded as noise adaptation. From Eq. 5 it is seen that such adaptation would follow the precise slope 0.5 only when spatio-temporal summation ($A_S t_i$) stays constant. In fact, it does not. In frog ganglion cells, integration time (t_i) falls as the power 0.17 of background intensity (Donner, 1987). In human psychophysics, spatio-temporal summation ($A_S t_i$) decreases as the power 0.25 of background intensity (Barlow, 1958). The decrease in t_i alone would, according to Eq. 5, give a limiting slope $(0.17 \times 0.5) + 0.5 \approx 0.59$ for noise adaptation measured with step stimuli. Dowling and Ripps (1977), using 1-s stimuli (steps, in effect), report limiting slopes of 0.5–0.7 for the adaptation of ganglion cells, b-wave, and the proximal negative response in the skate. Extended increment threshold slopes of 0.5–0.7 are found with step stimuli in cat ganglion cells as well. Barlow and Levick (1976) report a mean slope of 0.59 for 0.29°, 1 s (i.e., small-spot step) stimuli in ON-center cells. Sakmann and Creutzfeld (1969) obtained the mean slope 0.68 in cat ganglion cells, but they averaged results with spot sizes ranging from 0.2° to 1°, and it is possible that their largest spots had activated surround antagonism.

The Mechanism of Noise Adaptation

The site of adaptation. The adaptation of horizontal cells faithfully followed that of the rods, as also found in skate by Green et al. (1975). In bipolar cells of the dogfish retina, Ashmore and Falk (1982) found that the root-mean-square membrane fluctuations in the frequency band of photoresponses grew as the square root of the intensity of weak backgrounds (i.e., in proportion with the quantal fluctuations). If the mechanism for noise adaptation resided in the distal retina, it should be evident in these second-order cells: (*a*) they should desensitize at lower background intensities than rods, and (*b*) their membrane noise should increase less than proportionally to the quantal fluctuations (because the response to quantal fluctuations would be subject to decreasing amplification). Thus, these results indicate that the mechanism for noise adaptation resides in the proximal retina, conceivably involving interactions between bipolar, amacrine, and ganglion cells in the inner plexiform layer (cf. Dowling, 1967; Dowling and Ripps, 1977). Teleologically, it would appear purposeful to place the gain reduction close to the retinal output, where it can act on the entire retinal noise.

The adapting signal. The above-mentioned result of Ashmore and Falk (1982) also implies that, at least in dogfish, fluctuations proportional to the quantal noise do actually constitute a sustained input to third-order neurons. There is thus the intriguing possibility that the desensitizing mechanism responsible for noise adaptation is driven by the fluctuations themselves rather than through some accurate computation (as expressed by Eq. 5) from a DC signal proportional to the mean level of illumination.

The time course of adaptation. The idea that the gain of the proximal desensitizing mechanism could be set by the variation (standard deviation) rather than the mean of the background-induced signal is consistent with the slow time course of

ganglion cell adaptation to dim backgrounds. If it is assumed, for example, that a "steady" adaptation level requires that the adapting signal be known within ±10% with 95% confidence, a mean event number 500 (typical for a sensitivity-halving background summed over $A_S t_i$ in a toad ganglion cell; see Copenhagen et al., 1987) will be known accurately enough from one single sample. Since a sample in this case is the count within one integration time (mean, 1.76 s), the ganglion cell would need no more than 1 or 2 s for this. In contrast, knowing the standard deviation with the same accuracy requires 100–200 samples. With the mean integration time 1.76 s, this corresponds to 3–6 min.

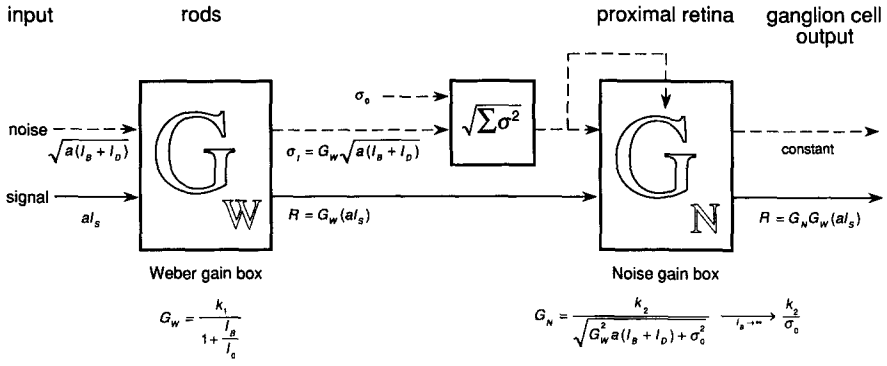

FIGURE 7. Schematic picture of the proposed two-level light adaptation involving a "Weber" gain box in the rods, and a "noise" gain box in the proximal retina. The passage of signal (*continuous arrows*) and that of noise (*broken arrows*) through the retina are drawn separately only for visual clarity; it should be noted that the arrows do not represent separate "channels"! (*Symbols*) Variables: G_W, gain of Weber box; G_N, gain of noise box; I_S, stimulus intensity; I_B, background intensity, σ_I, standard deviation of the noise component due to quantal fluctuations; R, response amplitude at each respective level in the retina. Constants: I_D, "dark" rate of isomerization-like events (≈0.03 Rh*s^{-1}); I_0, sensitivity-halving background for rods (≈1 Rh*s^{-1}); σ_0, standard deviation of neural noise in the frequency band of photoresponses; k_1 and k_2, proportionality constants. a stands for the spatio-temporal summation of the ganglion cell ($a = A_S t_i$) and may here be thought of as a constant, although strictly speaking it is not (see Text). The gain of the Weber box G_W is constant ($=k_1$) for very dim backgrounds, but falls as k_1/I_B when $I_B \gg I_0$. The gain of the noise box G_N is set by the total retinal noise, measured by the standard deviation $\sqrt{\sigma_I^2 + \sigma_0^2}$. For dim backgrounds, G_N is essentially determined by $k_2/\sigma_I \approx k_2/\sqrt{I_B}$. For bright backgrounds, however, G_W and consequently σ_I become very small; then G_N approaches the constant value k_2/σ_0 and the ganglion cell's response $R = G_N G_W(aI_S)$ will be governed by the Weber gain G_W alone.

Indeed, in the present experiments, rod adaptation to a new background was complete within a couple of seconds (Fig. 2). The ganglion cells, on the other hand, reached a stable level only several minutes after a change in background intensity (Fig. 5). A comparatively slow time course seems to be a general feature of proximal adaptation (frog ganglion cells: Byzov and Kusnezova, 1971; skate ganglion cells, b-wave and proximal negative response: Green et al., 1975; Dowling and Ripps, 1977).

Conclusion: Ganglion Cell Increment Thresholds Determined by Two Adaptation Mechanisms

At low background intensities, before rods start adapting, ganglion cells desensitize as if sensitivity is limited by the quantal noise from the background light (slope $\approx$ 0.5). At high background intensities, the desensitization of anuran rods and ganglion cells approximates Weber's law (slope 1, although the actual slopes are often somewhat shallower; cf. Hemilä, 1977; Donner, 1981; Leibovic et al., 1987). Under Weber adaptation, the sensitivity of the ganglion cell is clearly not limited by quantal fluctuations, but it might still be interpreted as noise-limited. The fact that ganglion cell adaptation follows the response amplitude of the rods could be due to a constant (background-independent) "neural" noise against which the rod photoresponse has to be detected. It is to be expected that the quantal noise shall, from some point, fall below such a constant noise level as background is raised. If rods desensitize as the power 1 of background intensity while quantal fluctuations increase as the power 0.5, the rod noise component that is due to these fluctuations will decrease as the power 0.5 of background intensity.

Fig. 7 schematically summarizes the two-step adaptation we propose. There is a distal "Weber" gain box in the rods, which, starting from background intensities around 1 Rh*s^{-1} (denoted I_0 in the figure), attenuates all light-induced signals (including those from quantal fluctuations) in inverse proportion to the prevailing (mean) background intensity. Between the rod output and the ganglion cell output, there is a second, "noise" gain box, the gain of which (G_N) is inversely proportional to the standard deviation of the noise in the frequency band of photoresponses, averaged over periods of a few minutes. In darkness, that noise predominantly stems from the quantal fluctuations of the intrinsic "dark light" I_D ($\approx$0.03 Rh*s^{-1} in the toad; Baylor et al., 1980). For 0.03 Rh*s^{-1} < I_B < 1 Rh*s^{-1}, there is a range of background intensities where the Poisson variation in the numbers of photoisomerizations from the background light is the dominant noise term, so the noise gain box follows $1/\sqrt{I_B}$ (square-root law, see Eq. 5). For $I_B \gg 1$ Rh*s^{-1}, the quantal fluctuations from both dark light and background light will become insignificant, because the neural signals they engender are so strongly attenuated by the Weber gain box of the rods. The dominant noise term is then due to a background-independent neural noise (the standard deviation denoted σ_0 in Fig. 7), and the noise gain box will be fixed at a constant value proportional to $1/\sigma_0$. In this range of background intensities, Weber adaptation alone will dominate the ganglion cell output.

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