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Transmission of scotopic signals from the rod to rod-bipolar cell in the mammalian retina

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Abstract

Mammals can see at low scotopic light levels where only 1 rod in several thousand transduces a photon. The single photon signal is transmitted to the brain by the ganglion cell, which collects signals from more than 1000 rods to provide enough amplification. If the system were linear, such convergence would increase the neural noise enough to overwhelm the tiny rod signal. Recent studies provide evidence for a threshold nonlinearity in the rod to rod bipolar synapse, which removes much of the background neural noise. We argue that the height of the threshold should be 0.85 times the amplitude of the single photon signal, consistent with the saturation observed for the single photon signal. At this level, the rate of false positive events due to neural noise would be masked by the higher rate of dark thermal events. The evidence presented suggests that this synapse is optimized to transmit the single photon signal at low scotopic light levels.

Keywords: Retina; Synaptic transmission; Single photon; Photoreceptor; Visual threshold; Scotopic vision

1. Introduction

Many mammals have evolved excellent night vision, and can perform well at scotopic light levels that produce photoisomerizations in only one out of thousands of rod photoreceptors. At such low light levels, vision is mediated by a specialized rod pathway comprising several stages of synaptic convergence to increase effective signal gain (Bloomfield & Dacheux, 2001; Sharpe & Stockman, 1999). Convergence reduces the half-saturating light intensity in a dark-adapted retinal ganglion cell by several orders of magnitude compared to a single dark-adapted rod (Copenhagen, Hemila, & Reuter, 1990). However, convergence can also dramatically increase the neural noise levels, because the tiny signals produced by single photons are carried by only a few neurons, whereas all the rods and postreceptoral neurons in the pool generate noise. Here we will review recent experimental results derived mainly from the mouse retina that helps to explain how the effects of the convergent neural noise are obviated during scotopic signaling.

Under scotopic conditions, the visual system must be sensitive enough to signal absorption of a single photon (Hecht, Schlaer, & Pirenne, 1942). Transduction of single photons is accomplished by the rod photoreceptors, which produce a hyperpolarization of about 1 mV for each photon (Schneeweis & Schnapf, 1995), with an integration time of about 320 ms (Tamura, Nakatani, & Yau, 1991). The transduction machinery in rod outer segments has evolved to limit the variability in both the amplitude and duration of the single photon signals, thus improving the signal-to-noise ratio (S/N) (Rieke & Baylor, 1998a, 1998b). The S/N ratio is defined as

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the peak amplitude divided by the standard deviation of the baseline noise. The single photon signal has also been observed in the rod bipolar cell (RBC), and is estimated to have a peak amplitude of ~6 pA, a time to peak of 135 ms, and an integration time of 140 ms (Berntson, Smith, & Taylor, in press). Such single photon signals have not been observed in the other interneurons in the rod pathway, but are hypothesized to be passed into cone circuits, and ultimately generate activity in the ganglion cells, the output of the retina. Direct estimates in cat indicate that a single rhodopsin isomerization in a rod will generate about three additional spikes in a ganglion cell (Barlow, Levick, & Yoon, 1971). In psychophysical experiments, visual threshold increases with the square root of the ambient light intensity, suggesting that the threshold is set by the statistical fluctuations in the number of single photon events detected (Barlow, 1957; Sakitt, 1972). Thus, the visual system is able to determine the rate at which single photons are absorbed, and to discriminate changes in that rate.

Single photon detection in rods has a low but significant error rate. Even in the complete absence of light, rods spontaneously produce events identical to the single photon signal (Ashmore & Falk, 1982; Baylor, Matthews, & Yau, 1980). These dark events (or thermal events) are attributed to thermal isomerization of the visual pigment. The rate at which thermal events occur, and the convergence of rod signals within the retina, predict the presence of a "dark light" in retinal ganglion cells (Barlow, 1956, 1957; Barlow & Levick, 1969). The thermal rate in mammalian rods is $\sim 0.01\,s^{-1}$ (Baylor, Nunn, & Schnapf, 1984). The predicted intensity of the dark light in the ganglion cells agrees reasonably with the equivalent dark light inferred from psychophysical experiments to limit our sensitivity to the dimmest light stimuli (Barlow, 1957; Schneeweis & Schnapf, 2000), suggesting that absolute visual threshold is ultimately limited by the thermal stability of rhodopsin.

This view may not be entirely accurate, because thermal events are not the only source of noise in rods (Lamb, 1987). Noise is also generated downstream of the photoisomerization reaction, and arises within the G-protein coupled signaling cascade responsible for phototransduction. This noise is referred to as continuous dark noise. Since the biochemical cascade controls the activity of cation channels in the outer segment, the continuous dark noise is manifest as voltage or current noise in the rod. Although the amplitude of the elementary events that generate the continuous dark noise is much lower than the thermal events, the frequency is much higher, and therefore the continuous noise could produce peak voltage fluctuations with amplitudes comparable to the single photon signal. The power spectrum of the continuous noise is very similar to the power spectrum of single photon responses (Baylor et al., 1980), and is thought in toad rods to arise from spontaneous activation of the phosphodiesterase (Rieke & Baylor, 1996). The S/N ratio for the single photon signal has been estimated at about 3 in mouse (Field & Rieke, 2002) and 5–7 in monkey rods (Schneeweis & Schnapf, 2000). Thus it is likely that the continuous noise contributes to the psychophysical dark-light, and may help limit the absolute visual threshold (Levick, Thibos, Cohn, Catanzaro, & Barlow, 1983).

As noted above, spatial integration through synaptic convergence greatly increases the sensitivity of consecutive stages in the rod pathway. The rod pathway comprises four synaptic connections as illustrated in Fig. 1. There are two main points of convergence; 20–50 rods converge upon each rod bipolar cell (RBC), and 20–25 RBCs converge upon each AII amacrine cell. Convergence from the AII amacrine cells to ganglion cells is more limited. However, even on-beta ganglion cells, with the smallest receptive fields in cat, receive input from 5 AII amacrine cells via cone bipolar terminals. Overall, signals from a thousand or more rods converge upon a single ganglion cell (Smith, Freed, & Sterling,

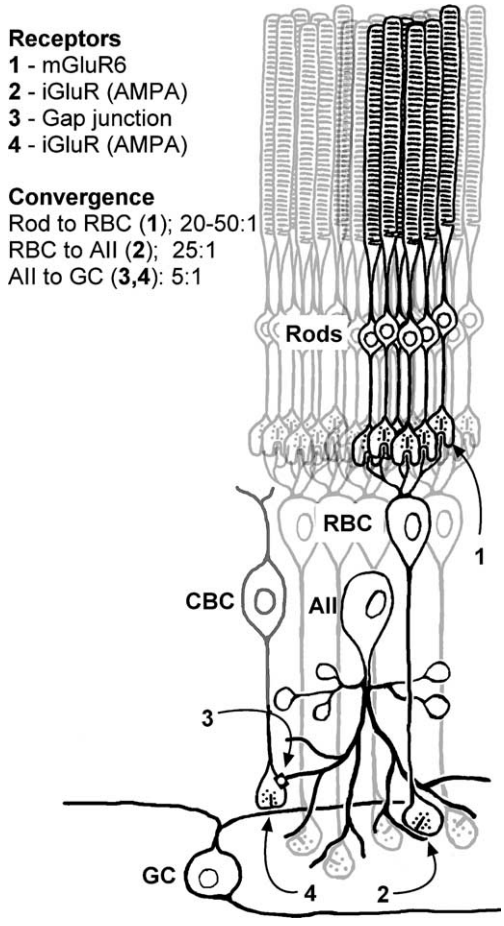

Fig. 1. Convergence within the rod pathway mediating scotopic vision. RBC: rod bipolar cell; CBC: on-type cone bipolar cell; AII: rod amacrine cell; GC: ganglion cell.

1986; Sterling, Freed, & Smith, 1988; Strettoi, Dacheux, & Raviola, 1990; Tsukamoto, Morigiwa, Ueda, & Sterling, 2001; Vaney, Young, & Gynther, 1991). In addition to increasing the signal amplitude, synaptic convergence increases the noise. If the inputs were summed linearly, the uncorrelated noise would increase with the square-root of the number of inputs. At scotopic backgrounds, when only one rod contributes a single-photon signal, linear summation will reduce the S/N ratio in the RBC by a factor of 4–7 and the noise would completely obscure the single photon signal (Baylor et al., 1984). Such considerations lead to the suggestion that there must be a non-linearity in synaptic transmission to reduce the effects of convergent noise. In the remainder of this review we will briefly summarize the properties of synaptic transmission from rods to RBC and outline the mechanisms that allow a synaptic non-linearity to reduce convergent noise.

2. The synapse between rods and RBCs

The dendrites of RBCs make invaginating contacts with rods (Fig. 2). The dendritic tip of the RBC penetrates a deep pocket at the base of the rod terminal, and terminates close to the synaptic ribbon, a specialized presynaptic structure at the site of vesicle fusion (Gray & Pease, 1971; Rao-Mirotznik, Harkins, Buchsbaum, & Sterling, 1995). The rod terminal completely ensheathes the dendritic tip, and therefore physically isolates it from adjacent dendritic tips. The glutamate released from the rod binds to mGluR6 receptors, which are localized beneath the dendritic tips (Nomura et al., 1994; Vardi, Duvoisin, Wu, & Sterling, 2000; Vardi, Morigiwa, Wang, Shi, & Sterling, 1998). The mGluR6 receptors close non-selective cation channels (de la Villa, Kurahashi, & Kaneko, 1995; Nawy & Jahr, 1991; Shiells & Falk, 1990; Yamashita & Wässle, 1991) by activating a postsynaptic signaling cascade that involves activation of $G_{0\alpha}$ (Dhingra et al., 2000; Nawy, 1999), which is concentrated in the dendritic tips of the RBCs (Huang et al., 2003; Vardi, 1998). A light stimulus suppresses glutamate release and allows the mGluR6 receptor-gated channels to open, thereby depolarizing the RBC (Berntson & Taylor, 2000; Euler & Masland, 2000). The coupling between the mGluR6 receptors and the channels involves significant biochemical amplification, since the dose-response relationship displays a Hill coefficient greater than one (Sampath & Rieke, 2004; Shiells, 1994; Shiells & Falk, 1994). The high postsynaptic gain is most likely a key mechanism for noise suppression and will be discussed further (van Rossum & Smith, 1998).

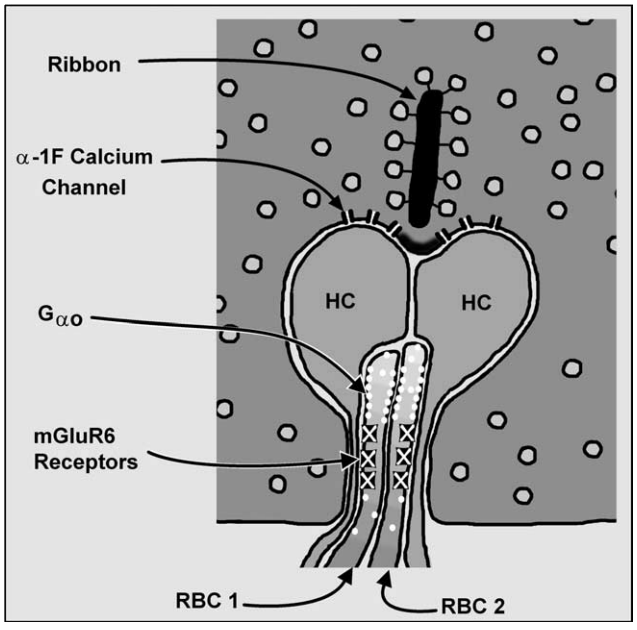

Fig. 2. Rod to RBC synapse. Each rod receives invaginating contacts from two RBC dendrites, and two horizontal cell dendrites (HC). The α-1F calcium channels that mediate transmitter release are localized in the presynaptic membrane close to the ribbons (Morgans, 2001). Glutamate release occurs from active zones at the base of the ribbon, and binds to mGluR6 receptors (X's) that are located below the tips of the dendrites (Nomura et al., 1994; Vardi et al., 2000). The G-protein, $G_{\alpha 0}$ is distributed throughout the rod bipolar cells but is most highly concentrated in the dendritic tips (Huang et al., 2003; Vardi et al., 2000). The identity and location of the channels gated by mGluR6 are unknown.

The physical separation afforded by the invaginating contacts and the prevalent extra-synaptic glutamate reuptake (Grünert, Martin, & Wässle, 1994; Rauen, Taylor, Kuhlbrodt, & Wiessner, 1998) suggest that each dendritic input responds only to transmitter released from a single rod, independent of signals in adjacent dendritic tips. The *postsynaptic* responses in adjacent dendritic tips are also likely to be independent because diffusion of large molecules along a dendrite is slow, on the order of 4 μm over the duration of a rod response (200 ms) (Helmchen, 1999). The effector channel for the mGluR6 receptors has not yet been identified or localized, and the intermediaries between $G_{0\alpha}$ and the channel are unknown. Therefore, although we argue below that the inputs act independently, biochemical convergence of the synaptic inputs within the RBC by diffusion of a small second messenger molecule cannot be excluded.

As in other synapses, calcium triggers the vesicle fusion that releases transmitter from rod terminals. Calcium flows into the terminals through retina specific α-1F calcium channels (Bech-Hansen et al., 1998; Morgans, Gaughwin, & Maleszka, 2001), that are tonically activated at −40 mV, the dark resting potential of rods (Schneeweis & Schnapf, 1995). Rod terminals contain synaptic ribbons, which are thought to be important for maintaining a steady release of vesicles in darkness (Gray & Pease, 1971; Morgans, 2000).

Similar to salamander and toad retina (Attwell, Borges, Wu, & Wilson, 1987; Belgum & Copenhagen, 1988), the rod to RBC synapse in mouse truncates the rod signal, because a dark-adapted rod half saturates at about 30–100 Rh* (Baylor et al., 1984; Schneeweis & Schnapf, 1995; Tamura et al., 1991), whereas the RBC half saturates at 0.7–3 Rh*/rod. This difference suggests that the synapse is optimized for single photon transmission, particularly in the case where it saturates for a single photon. If vesicle release is stochastic, fluctuations in the rate might slow release long enough to erroneously signal detection of a photon. To constrain such false events to an acceptable rate, modeling studies have shown that, if a single photon could halt release completely, then the rate of Poisson release from each terminal must be about 100 vesicles/s (Rao-Mirotznik, Buchsbaum, & Sterling, 1998; van Rossum & Smith, 1998). However, this scheme would only work if the synapse could completely halt release for absorption of a single photon, which seems unlikely given our present understanding of transmitter release from photoreceptors.

During depolarization above the activation threshold, the open probability of the calcium channels that mediate transmitter release from mammalian cones increases e-fold over a 6 mV change in the membrane potential (Taylor & Morgans, 1998). In expression systems the rod α-1F calcium channel displays a similar voltage dependence, although its half-maximal activation potential is about 30 mV more positive than in native systems (Baumann, Gerstner, Zong, Biel, & Wahl-Schott, 2004; Koschak et al., 2003; McRory et al., 2004). Assuming that native α-1F channels activate in the appropriate range, a single photon event with a peak amplitude of 1 mV would reduce the number of open calcium channels by ~20%. At a vesicle release rate of 100/s, this incomplete suppression of the calcium current would modulate the number of vesicles by an insufficient number of events to reliably transmit the photon signal as a separate event (S. Schein, personal communication). One possible remedy is that cooperative binding of calcium ions to the release machinery amplifies the calcium sensitivity of release. However, vesicle release is thought to depend linearly on calcium influx (Thoreson, Tranchina, & Witkovsky, 2003; Witkovsky, Schmitz, Akopian, Krizaj, & Tranchina, 1997). A second possibility is that Poisson release by the rod is much faster, e.g. 800 vesicles/s, giving a more reliable indication of a photon. Such a high rate seems unsustainable by the rod in the dark because the number of vesicles docked to the ribbon and nearby in the terminal is insufficient (Rao-Mirotznik et al., 1995). A third possibility is that release by the rod is more regular than Poisson (de Ruyter van Steveninck & Laughlin, 1996; van Rossum & Smith, 1998, S. Schein personal communication). Clearly it will be important to determine the calcium dependence and statistics of vesicle release from the mammalian rods.

3. The single photon threshold is postsynaptic

Thermal events are identical to events initiated by a photon, so they represent an irreducible noise source. Therefore, to detect dim stimuli, the visual system must resolve an increase in the rate of single photon events above the background rate of thermal events. This implies that mechanisms to reduce convergent noise are only useful if they selectively suppress the continuous and synaptic noise. One type of temporal filtering during synaptic transmission that could optimally extract the single photon signal from the noise is matched filtering (Baylor et al., 1984; Bialek & Owen, 1990). For a matched filter the synaptic transfer function is precisely matched to the frequencies represented in the single photon signal. More generally, temporal filtering can reduce noise, and improve temporal resolution by suppressing low and high frequency noise (Armstrong-Gold & Rieke, 2003; Copenhagen, Ashmore, & Schnapf, 1983). While temporal filtering could reduce the high frequency noise associated with vesicle release, or channel gating, it could not obviate the effects of continuous noise because the temporal components of the continuous noise are very similar to the single photon signal. Therefore, temporal filtering can remove some but not all of the noise associated with synaptic transmission of single photon signals.

Two recent papers (Berntson et al., in press; Field & Rieke, 2002), examining signal transmission from rods to RBCs in mouse retinal slices have proposed that synaptic transmission involves a threshold non-linearity, in which subthreshold continuous noise is not transmitted through the synapse, while single photon events that exceed the threshold are transmitted, as suggested by van Rossum and Smith (1998). The threshold is unlikely to be presynaptic, since off-cone bipolar cells that receive direct input from rods (Hack, Peichl, & Brandstatter, 1999; Soucy, Wang, Nirenberg, Nathans, & Meister, 1998; Tsukamoto et al., 2001) do not display a nonlinearity (Field & Rieke, 2002). The threshold is envisaged to result from the high signal transduction gain of the postsynaptic mGluR6 receptors, which results in a sharp threshold-like transition from saturation to conduction (Shiells & Falk, 1994). In the dark, despite fluctuations in glutamate release, driven in part by continuous noise, the mGluR6 transduction remains saturated and 97% of the ion channels remain closed (Sampath & Rieke, 2004). The hyperpolarization produced by a single photon suppresses glutamate release enough to relieve the saturation and produce a steep increase in the postsynaptic channel activity, resulting in a depolarizing single photon signal in the dendritic tip. The signals from individual dendrites are then summed

linearly at the RBC soma. Implicit in this model is the notion that the threshold is set independently in each dendritic tip connection (Sampath & Rieke, 2004; van Rossum & Smith, 1998), so that non-linear noise suppression precedes linear summation. While the two studies cited above both proposed such a postsynaptic non-linearity, important differences in the details remain to be resolved.

In particular, the two studies differed significantly in their assignment of the threshold level. Field and Rieke (2002) found that the number of null responses observed for dim flashes far exceeded that expected for a Poisson process, and they accounted for this by proposing a threshold level of 1.2 times the single photon event amplitude. This threshold would be optimal for event rates 10-fold lower than the dark thermal rate, and would produce a large increase in the S/N ratio in the RBC (~350×), resulting in the loss of 75% of the single photon events. Berntson et al. (in press), found that the responses to dim flashes essentially followed Poisson statistics, and they concluded that a threshold at about 0.85 times the single photon amplitude would be optimal. At this threshold, the number of false positive single photon events due to the thermal rate is expected to exceed false positives due to continuous noise by a factor of 2, while the number of single photon events lost is only 40%. Preservation of more events has important implications, as discussed below.

A second difference was in the linearity of the flash responses at low intensity. Field and Rieke (2002) found that the response amplitude increased supralinearly with flash intensity and fitted their data with the Hill equation with a Hill coefficient of 1.5 and a half-saturating intensity of 2.8 Rh*/rod. Berntson et al. (in press), found that the response amplitude increased linearly with flash intensity, and fitted their data with a saturating exponential with a half-saturating intensity of ~0.7 Rh*/rod. Given the synaptic arrangement, and the postulated postsynaptic non-linearity, both interpretations are plausible. If the synapse half-saturates at ~2.8 Rh*/rod, then each rod can signal >3 single photon events to the RBC. The RBC intensity-response relation is supralinear because the postsynaptic non-linearity produces a more than additive response when single photon events superimpose. For a half-saturating intensity of ~0.7 Rh*/rod, the rod to RBC synapses *saturate* when only 1 photon is absorbed per rod, which makes superposition of two single photon events impossible. In this case, consistent with observation, the maximum slope is predicted to be 1, since the RBC linearly sums the single photon events from each dendrite.

An additional component of the postsynaptic response, not considered in the above studies is calcium dependent negative feedback (Nawy, 2000; Shiells, 1999; Shiells & Falk, 1999; Snellman & Nawy, 2002). When the mGluR6 gated channels open they admit calcium ions, which bind to some component of the transduction machinery and inhibit mGluR6 signal transduction. In the salamander and dogfish, the inhibition develops with a time constant on the order of seconds, and can be blocked by the fast intracellular calcium chelator BAPTA (Nawy, 2004; Shiells & Falk, 1999). Since calcium feedback is negative, it has been proposed to play a role in light adaptation in the RBCs. We have found that postsynaptic calcium feedback in mouse rod bipolar cells is much faster, and can also be blocked by intracellular BAPTA (Berntson & Smith, Taylor in press). The feedback in mouse RBCs has time a constant ~60 ms, fast enough to reduce the duration of the flash response by about 50%. If the dendritic inputs from individual rods are isolated, as we have hypothesized, then the feedback acts upon the single photon response. The amplitude threshold in the RBC, followed by the high gain of the mGluR6 signal transduction will tend to increase the variability in the amplitude and time-course of the single photon signals. Fast negative feedback produced by calcium influx through the mGluR6 gated channels might be a potent mechanism for reducing the variability in the amplitude and time course of the single photon response, and thus improving the S/N ratio. Further experiments will be required to test these ideas.

4. The next stage—AII amacrine cells

The next neural stage in the rod pathway, the AII amacrine cell, receives convergent input from ~25 RBCs, so the synapse from the RBC must also include some mechanism for noise suppression (Smith & Vardi, 1995; Sterling et al., 1988). RBCs contact AII amacrine cells via AMPA receptors, which are unlikely candidates to generate a postsynaptic non-linearity. However, both synaptic release by the RBC and postsynaptic response in the AII are transient, with an impulse response shorter than the RBC single photon response (Singer & Diamond, 2003) factors that would tend to minimize dark release and also noise in the AII. In addition, AII amacrine cells generate TTX dependent action potentials (Boos, Schneider, & Wässle, 1993; Veruki & Hartveit, 2002), raising the possibility that a non-linear voltage threshold in the AII might allow it to selectively transmit single photon signals, while suppressing subthreshold noise (Smith & Vardi, 1995). Bipolar cell terminals, coupled to the AII amacrine cells through gap junctions (Mills & Massey, 1995; Xin & Bloomfield, 1999), would depolarize synchronously during an action potential and then produce a synchronous release of transmitter. The synchronous EPSPs transmitted to the ganglion cell would then trigger a burst of action potentials (Barlow et al., 1971; Mastronarde, 1983). These ideas remain to be tested experimentally.

The RBC and its synapse to the AII amacrine cell are noisy and contribute noise to the AII (Hartveit, 1999; Singer & Diamond, 2003), which would increase false positive single photon signals in the ganglion cell. Therefore, to reduce the fraction of false positives at the destination, it is important to preserve as many as possible of the real positive events from earlier stages of transmission. For this reason, a low threshold at the rod to RBC synapse that preserves a larger fraction of the real single photon events results in a more favorable S/N ratio at the ganglion cell. Thus the threshold at the rod to RBC synapse appears to be a compromise between lowering false positive and false negative rates in the presence of a background thermal event rate.

In summary, we would underscore two main conjectures; at scotopic light levels, the rod synapse saturates when transmitting a single photon, and, the high gain of the postsynaptic signal transduction produces a strong non-linearity that suppresses continuous dark noise. However, we have discussed evidence that the RBC synapse can operate in different modes: at high gain, saturating for a single photon (Berntson et al., in press) or at lower gain, saturating for multiple photons (Field & Rieke, 2002). In the high-gain mode, the rod synapse saturates at a flash strength of 1 Rh*/rod, with a non-linear threshold just high enough to remove most of the dark noise while losing only ~40–50% of the single photon signals. In the lower gain mode, it saturates at >3 Rh*/rod and the non-linear threshold rises to a point where most single photon signals are lost, resulting in a large increase in the relative gain for double-Rh*/rod signals, and an increase in the Hill coefficient for responses to weak flashes. Since the preparations in both studies were maintained in complete darkness, it is not clear how this difference arises, but it does suggest that the synapse is able to adjust its gain. This hypothesis is attractive because it underscores the need for the system to adapt to changing backgrounds to maintain optimal readout of photon signals. It will be important in future studies to identify the factors that underlie the difference in gain, and to determine whether such mechanisms contribute to normal light-adaptation.

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