

Setting the absolute threshold of vision

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Abstract

The performance of sensory systems in many cases is limited by the physical nature of the stimulus. For vision, the quantal nature of light limits detection by dark-adapted observers; only now are we beginning to be aware of the subtleties in the biophysical mechanisms underlying this exquisite sensitivity.

Introduction and context

We have known for over 60 years that a dark-adapted human observer can reliably identify a flash of light activating only a small subset of the photoreceptor cells [1,2]. A requirement for such exquisite sensitivity is that the individual rod photoreceptors must be able to produce a reliable signal in the ganglion cells, the cells that provide the output from the retina [3]. Many of the details of how the single-photon response is generated in the rods and how it is processed by retinal interneurons have remained in question. Over the past decade, several important advances have identified and characterized the mechanisms that preserve the single-photon responses amid intrinsic noise in the receptor cells and retinal circuitry.

Major recent advances

In response to an absorbed photon, rod photoreceptors generate small graded hyperpolarizations on the order of approximately 1 mV [4]. The challenge for retinal processing is to convey this small signal to higher visual centers in the presence of significant receptor noise. Efficient signal transmission through the retina is accomplished by means of a conserved and highly convergent pathway in the mammalian retina called the rod bipolar pathway [5,6]. This pathway uses an exclusive rod 'On' bipolar cell and a depolarizing (AII) amacrine cell to boost the single-photon response

amplitude and suppress noise, before feeding this signal back into the cone circuitry. The rod signals are then relayed to spiking ganglion cells, which in turn convey this information to the lateral geniculate nucleus and higher visual areas.

Rod phototransduction has received intense study over the past 30 years, but our understanding has deepened considerably with recent advances in mouse genetics that have facilitated the creation of mouse lines with selective perturbations in the signaling cascade. We are now beginning to see in detail how components of the signaling cascade contribute to properties of the single-photon response. These components include: (a) the role of Ca^{2+} feedback in the synthesis of cyclic guanosine monophosphate (cGMP), which limits rod noise and speeds the time course of the single-photon response [7,8]; (b) the role played by rhodopsin phosphorylation and arrestin binding in the shutoff of the single-photon response [9-11]; and (c) the role played by regulators of G-protein signaling (RGSs) proteins in accelerating the GTPase activity of the G-protein transducin [12,13].

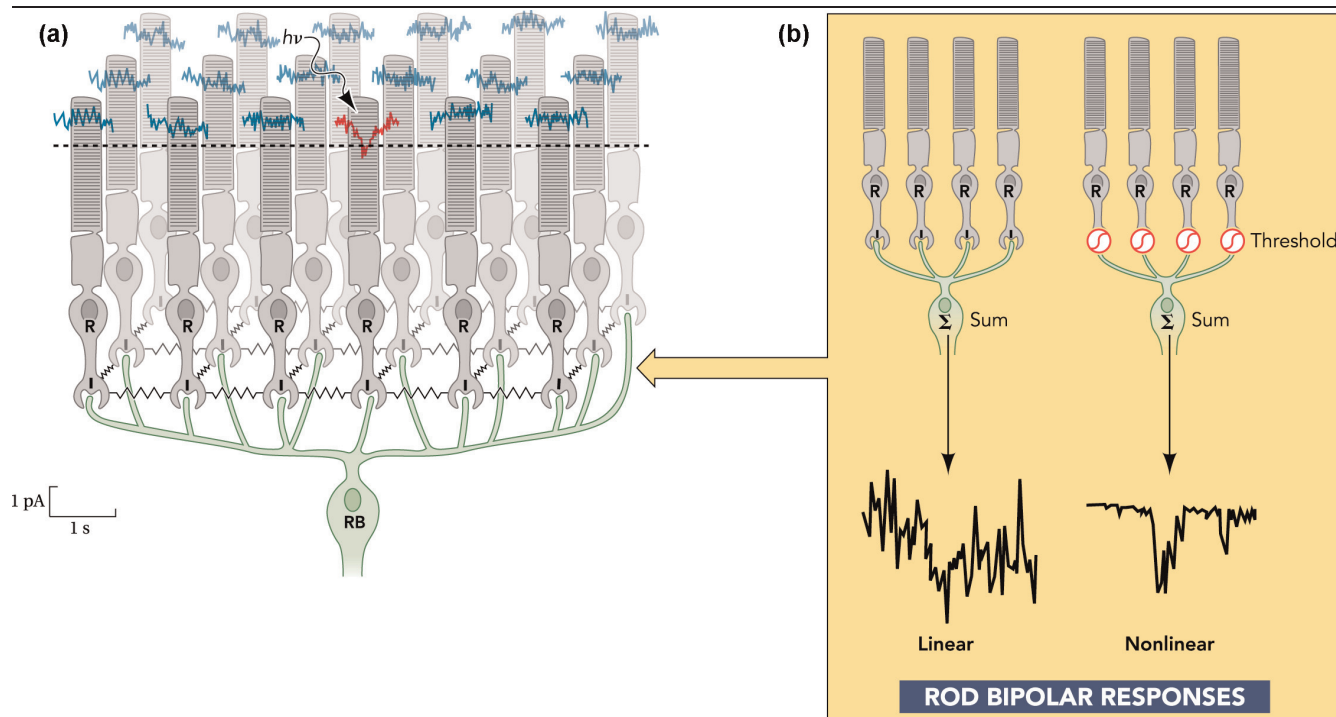
Advances in our understanding of rod synaptic transmission have also revealed specializations for the transmission of the single-photon response. Rod photoreceptors expend considerable energy to maintain a depolarized

membrane potential in darkness [14] which sets synaptic Ca^{2+} channels near the steepest point in the relationship between membrane potential and Ca^{2+} influx [15]. Proteins like calcium-binding protein 4 (CaBP4) [16] have been implicated in the further fine-tuning of this voltage dependence to allow small changes in membrane potential to produce proportionally larger changes in Ca^{2+} concentration in the presynaptic terminal, which in turn results in a larger change in glutamate release [17].

While the factors that control the size and time course of the single-photon response and of glutamate release have been studied in detail, light detection will ultimately depend on how the system is able to discriminate the single-photon response from noise. Studies of phototransduction have identified two major sources of noise that limit the detection of single photons: the thermal activation of rhodopsin, which generates 'discrete' noise events, and the spontaneous activity of the cGMP phosphodiesterase (PDE), which generates 'continuous' noise [18,19]. Either of these

forms of noise can produce fluctuations in cGMP that resemble the single-photon response. The key to light detection is therefore the ability of our visual system to discriminate light-driven signals from these two forms of noise. The rod-to-rod bipolar synapse plays a key role in this process. In particular, a threshold-like nonlinearity at this synapse [20,21] is positioned to make an optimum separation of the single-photon response from continuous noise [22]. As shown in Figure 1, this threshold-like nonlinearity acts at every rod-to-rod bipolar synapse to allow only signals that exceed a criterion amplitude to pass through the synapse, so that only the largest responses from the rods can be reliably detected by the bipolars. Rod bipolars are thus able to sum responses from rod photoreceptors in a manner that allows them to preserve the larger single-photon responses while rejecting much of the continuous noise component. Such an operation is believed to improve the signal-to-noise ratio of the single-photon response in rod bipolar cells by more than 300-fold over what we would expect from a linear combination of rod signals [22].

Figure 1. Convergence and threshold-like nonlinearity at the rod-to-rod bipolar synapse

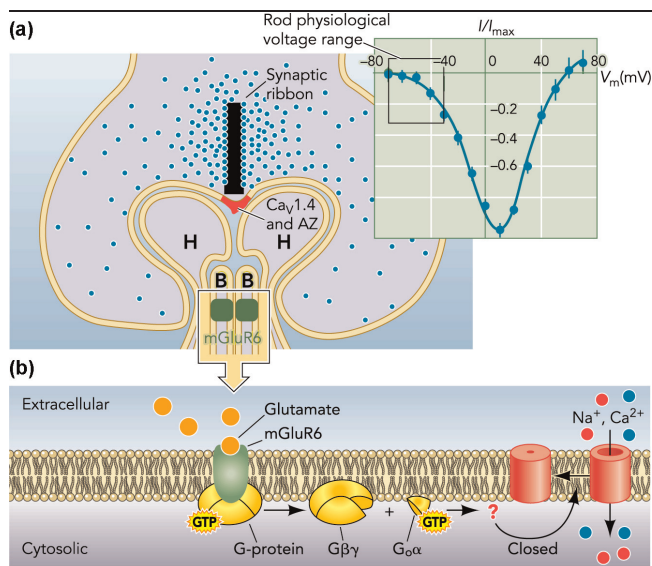


(a) A rod bipolar cell pools inputs from many rods, but near absolute visual threshold, only one rod may absorb a photon (red) while the remaining rods are generating electrical noise (blue). A threshold-like nonlinearity (dashed) improves photon detection at this synapse by retaining responses that exceed threshold (red) in rods most likely absorbing a photon, while discarding responses that do not exceed threshold and that are more likely noise in the remaining rods. **(b)** Nonlinear signal processing can improve the fidelity of rod signals. If rod outputs from **(a)** are simply summed, the resulting trace is noisy, but when summed after applying the threshold-like nonlinearity for each rod in **(a)**, the response is easier to discern. R, rod; RB, rod bipolar cells. Reprinted with permission from *Physiology* [32]. Copyright 2007, The American Physiological Society.

Mechanistically, this threshold-like nonlinearity is generated by postsynaptic saturation at the rod-to-rod bipolar synapse [23]. This saturation appears not to be attributable to saturation of binding to metabotropic glutamate (mGluR6) receptors on the rod bipolar dendrites but seems instead to occur somewhere within the G-protein cascade that couples mGluR6 to cation channels.

Understanding how the nonlinear threshold is set by rod bipolar cells will ultimately require the elucidation of the mGluR6 signaling pathway in the bipolar dendrites. As shown in Figure 2, glutamate released from rods in darkness is sensed postsynaptically by mGluR6 receptors, which in turn activate a $G_{\alpha\alpha}$ -containing G-protein.

Figure 2. Structure and signal transfer at the rod-to-rod bipolar synapse



(a) The rod spherule is a specialized invaginating structure where the dendrites of horizontal (H) and rod bipolar (B) cells are apposed to glutamate release sites controlled by a synaptic ribbon. Ca^{2+} channels ($Ca_v1.4$) located near the active zone (AZ) allow the continuous release of glutamatergic vesicles in darkness. In 'On' rod bipolar cells, glutamate is sensed by metabotropic glutamate receptor type 6 (mGluR6) receptors located near the mouth of the invagination. **Inset:** Release of glutamate is dependent on Ca^{2+} influx through Ca^{2+} channels, which is graded by voltage over the physiological range. **(b)** The signaling cascade in rod bipolar cell dendrites is poorly characterized. mGluR6 activation leads to the activation of $G_{\alpha\alpha}$, which through unknown mechanisms leads to the closure of nonselective cation channels, which may be in part TRPM1 (transient receptor potential cation channel, melastatin family, member 1). The light-evoked reduction in glutamate release relieves activity in this cascade and opens cation channels leading to membrane depolarization. Reprinted with permission from *Physiology* [32]. Copyright 2007, The American Physiological Society.

Through a series of unknown steps, the activity of this pathway leads to the closure of transduction channels, part of which may consist of TRPM1 [24,25], a member of the TRPM family of transient receptor potential (TRP) ion channels. Recent physiological evidence indicates that the properties of these channels are similar to those of other TRP channels—they can, for example, be gated by TRPV1 agonists [26]. Since postsynaptic saturation sets the position of the nonlinear threshold [23], elucidating the remaining transduction components will be key to identifying the components that set the level of synaptic saturation.

While the properties of signaling in the rod photoreceptors and rod bipolar cells have received much attention, other mechanisms downstream also play key roles in improving the fidelity of the single-photon response. For example, signals in AII amacrine cells are boosted by multivesicular release at the rod bipolar cell-to-AII amacrine cell synapse, increasing the discrimination of the single-photon responses from synaptic noise [27]. Furthermore, AII amacrine cells create an electrically coupled network that may suppress synaptic noise [28]. This network is formed by gap junctions consisting of connexin 36 and is critical for the transmission of high-sensitivity signals to ganglion cells [29] by means of efficient signal transmission to cone bipolar cells [30].

Future directions

Over the past decade, significant advances have been made that have helped us understand how signals are preserved and noise is eliminated in the rod circuitry in order to maximize the detection of the single-photon response. However, several key issues remain. For example, what type of noise is limiting detection? Is it the discrete noise due to thermal activation of rhodopsin, or the continuous noise produced by spontaneous PDE activation? In principle, either discrete or continuous noise could limit light detection by generating false-positive signals. Mechanisms such as the threshold-like nonlinearity at the rod-to-rod bipolar synapse may eliminate much of the rod noise, but the identification of the molecular mechanism that is responsible will require the elucidation of the mGluR6 signaling cascade in the rod bipolar dendrites.

One other area of future investigation will be the identification and characterization of the retinal pathways that carry rod signals to ganglion cells. While the rod bipolar pathway may function predominantly near absolute threshold, it saturates at light levels where the rods are not saturated. Under these conditions, rod signals may use alternative rod pathways to relay signals.

These include the rod-cone pathway [6] and the rod Off pathway [31], which are believed to relay signals for mesopic vision. The threshold and dynamic range of each pathway for relaying rod signals to ganglion cells remain to be determined.

Abbreviations

CaBP4, calcium-binding protein 4; cGMP, cyclic guanosine monophosphate; mGluR6, metabotropic glutamate receptor type 6; PDE, phosphodiesterase; RGSs, regulators of G-protein signaling; TRP, transient receptor potential; TRPM1, transient receptor potential cation channel, melastatin family, member 1; TRPV1, transient receptor potential cation channel, vallinoid family, member 1.

Competing interests

The authors declare that they have no competing interests.

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