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Post-Receptor Adaptation: Lighting Up the Details

The very first rays of the rising sun enrich our visual world with spectacular detail. A recent study reveals how retinal circuits downstream of photoreceptors 'functionally re-wire' to trade-off sensitivity for high spatial acuity during night–day transitions.

Robert G. Smith[1], Kerry R. Delaney[2], and Gautam B. Awatramani[2,*]

We experience a very different visual world in the night and day. This is because images falling on the rod and cone photoreceptors are generally of poorer quality in the night compared to the day and are processed by downstream circuits in the retina in distinct ways [1–3]. In its marvellously compact design, however, many circuit elements of the retina that process night and day vision are shared [3]. How a hard-wired retinal circuit can process information differently under widely varying conditions is a question that has fascinated many vision researchers over the years.

A growing body of literature suggests that retinal circuits can 'functionally re-wire' to execute different processing strategies required for optimization of our visual experiences under varied ambient light conditions. A number of previous studies have documented light-dependent functional changes in the *inhibitory* circuitry controlling output ganglion cells [4–7]. A new study by Grimes *et al.* [8] provides evidence that light-dependent changes may originate in *excitatory* bipolar cells and offers clear mechanistic insights into how these cells are functionally modified to optimize circuit function under different ambient illuminations.

Synaptic Release Properties of ON Cone Bipolar Cells Are Modulated by Ambient Light

Bipolar cells, which connect photoreceptors to retinal ganglion cells, come in two main flavours: 'ON' cells, which are activated by light increments and 'OFF' cells, which are activated by light decrements. Grimes *et al.* [8] made the striking observation that ON bipolar cells can dynamically change their behaviour, to act either collectively under dim light conditions or as independent subunits during the bright day. This allows downstream ON alpha retinal ganglion cells to trade sensitivity for spatial resolution, according to the ambient light conditions.

The authors found that, under dim light conditions, individual ON cone bipolar cells increase and decrease their neurotransmitter release in linear proportion to changes in light intensity (Figure 1B, left). The amount of neurotransmitter released from bipolar cells was estimated by monitoring excitatory postsynaptic currents in voltage-clamped ON alpha retinal ganglion cells. When presented with large stimuli, the simultaneous activity of many ON cone bipolar cells was effectively summed over the ON alpha retinal ganglion cell's receptive field. However, edges (Figure 1A) or complex images failed to modulate responses of ON alpha retinal ganglion cells. Although individual bipolar cells respond well to such stimuli (Figure 1B, left), as a direct consequence of their linear properties, the simultaneous increases and decreases in excitation produced by light and dark aspects of images falling over different ON bipolar cells tended to cancel each other when summed by the ON alpha retinal ganglion cell (Figure 1B, left). Thus, under dim light conditions the linear behaviour of ON cone bipolar cells allows them to act collectively, driving responses with limited spatial resolution but with highest sensitivity — which is key under these conditions.

Unexpectedly, the overall release rate of transmitter from ON cone bipolar cells is reduced under bright conditions, and the behaviour of the circuit becomes decidedly nonlinear. Although output rises and falls with changes in light levels, it appears as a 'half-wave rectified' sine wave [9–11] (Figure 1B, right), since the release rate

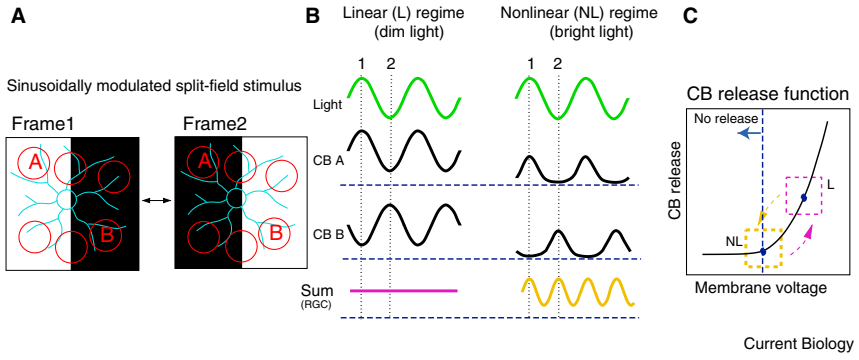

Figure 1. Ganglion cell input transitions from linear in the night to nonlinear in the day.

(A) An alpha retinal ganglion cell that receives many bipolar cell inputs (red circles) is stimulated with a sinusoidally modulated split-field stimulus centred over its dendritic tree. (B) A model showing the expected transmitter output rates of individual ON cone bipolar cells (CB A, CB B; black traces) under dim ambient illumination (dashed horizontal blue lines indicate no output). Two cells (CB A and CB B) located on opposite sides of the ganglion cell are stimulated by opposite phases of the sinusoid. The green sinusoidal trace indicates the time-dependent variation in light intensity over CB A. Since CB responses are linear, their summed inputs to the retinal ganglion cell results in a spatially unmodulated response (magenta trace; bottom left). When the background was brightened, the output of ON cone bipolar cell responses became non-linearly rectified — bipolar cells released transmitter during the brightening phase of the stimulus, but did not respond to the dimming phase (lower half-cycles); resulting in a 'half-wave rectification'. The spatially offset cone bipolar cells (CB A and CB B) caused the ON alpha retinal ganglion cell to respond twice for every stimulus cycle — their response was frequency-doubled — indicating the emergence of circuit nonlinearities. (C) The cone bipolar cell release function predicts linear or non-linear output of the ON cone bipolar cell under different ambient illuminations. Under dim light conditions cone bipolar cells are relatively depolarized and their membrane potential fluctuates along the linear part of the release function curve (box labelled 'L'), giving rise to responses that fully capture the increments and decrements in luminance when modulated sinusoidally (B, left). Under bright light conditions, cone bipolar cells hyperpolarize and shift to the nonlinear part of the release function curve (box labelled NL), giving rise to a rectified response (B, right).

from individual bipolar cells cannot drop below zero. In other words, neurotransmitter release from ON cone bipolar cells is no longer linearly proportional to luminance (Figure 1B, right). Consequently, the ON alpha retinal ganglion cell now receives spatially varying signals from bipolar cells as the simultaneous stimulation of multiple ON cone bipolar cells by bright and dim aspects of the image do not cancel each other (as they did in dim light conditions). Thus, under bright conditions, the collective summation of bipolar cell signals breaks down, compromising sensitivity. In this regime, bipolar cells can perform as independent elements to increase the spatial acuity of downstream ganglion cells: ON alpha retinal ganglion cells now respond to edges and to complex stimuli.

These findings have profound implications for our understanding of the function of retinal circuits. Classically, studies in cat have shown linear summation or nonlinear summation to be a property of separate circuits mediated by X and Y types of ganglion cells, respectively [9–12]. Moreover, linear summation by X type ganglion cells distinguishes them from the nonlinear summation shown by the Y type over a wide range of light intensities [13]. However, Grimes *et al.* [8] found that, in mouse retina, a single class of ON alpha retinal ganglion cells (anatomically homologous to cat Y cells) exhibit either linear or non-linear summation, depending on the background illumination. This suggests that different species have fundamentally different processing strategies. Moreover, these findings may also explain why it has been difficult to classify ganglion cells in the mouse retina based on their summation properties [14]. Thus, retinal circuits may exhibit more flexibility in their computational abilities than previously envisioned.

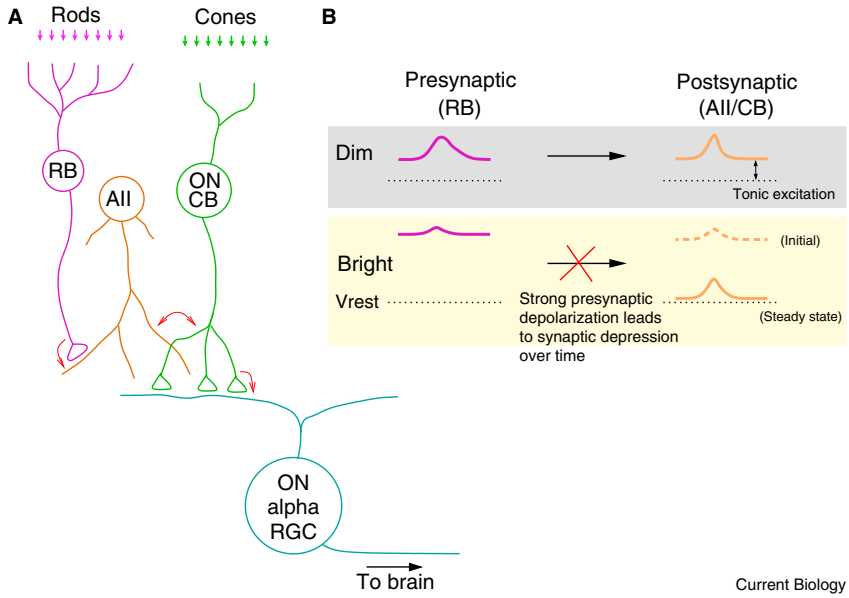

Figure 2. Circuitry underlying modulation of linearity in the ON-alpha ganglion cell from night to day.

(A) Schematic showing the convergence of rod and cone signals at the ON cone bipolar cell terminals. At night, rod signals are collected by the rod bipolar (RB) cell and are transmitted to the AII amacrine cell, which then passes them through a gap junction (double-ended arrow) to ON cone bipolar cells (CB), where they are transmitted to ganglion cells. In daylight, cone signals are collected by cone bipolar cells and are transmitted directly to ganglion cells.
(B) In moonlight, the RB cell is depolarized by several millivolts and releases neurotransmitter tonically, depolarizing the AII amacrine cell and coupled CBs. In daylight, ambient light further depolarizes the RB cell, which causes it to adapt after several seconds and stop releasing neurotransmitter. The decreased excitation leads to a steady-state hyperpolarization of the AII amacrine/ON cone bipolar cell gap junction coupled network.

Creating Non-linear Subunits through Ambient Light-dependent Membrane Hyperpolarization

Next, Grimes *et al.* [8] extended their ground-breaking findings to reveal how ambient light transforms linear bipolar cell output responses into non-linear ones. To do so, they undertook the Herculean task of recording responses to steady-state light increments in different elements of the rod pathway (Figure 2A). Rods are known to activate a single type of ON bipolar called the rod bipolar cell, which transmits signals to intermediary AII amacrine cells via conventional glutamate receptors. AII amacrine cells then pass their signals directly to ON cone bipolar cell terminals via gap junctions. To access AII amacrine and ON cone bipolar cells that are sandwiched between the photoreceptor and ganglion cell layers, the authors prepared transverse retinal slices in the dark (with the aid of infrared night vision goggles) to preserve the adaptational state of the retina.

Direct recordings from rod bipolar cells, which express sign-inverting metabotropic glutamate 6 (mGluR6) receptors, revealed that light steps cause them to depolarize by 5–10 mV above the potential measured in the dark, consistent with rod photoreceptors remaining slightly hyperpolarized with reduced glutamate release (Figure 2B). Surprisingly, however, the AII amacrine cell, which is postsynaptic to the rod bipolar cell, initially depolarized when exposed to light, but then gradually hyperpolarized over a few minutes (Figure 2B). Previous studies have demonstrated that the rod bipolar-to-AII amacrine cell synapse is highly susceptible to synaptic depression [15,16]. Indeed, in bright light these authors directly measured a decrease in excitatory input to AII amacrine cells, implying that a steady state depolarization of the presynaptic rod bipolar cells leads to synaptic depression. Interestingly, as AII amacrine cells are directly electrically coupled via gap junctions to ON cone bipolar cells, they too hyperpolarized by 3–5 mV in response to brightening steps. This results because cone signalling to the ON cone bipolar cell dendrites quickly adapts to steady illumination, leaving the AII amacrine cells to dominate cone bipolar cell resting membrane potential through electrical coupling at their axon terminal.

On first thought, one would not imagine that a mild change in membrane potential would have a profound impact on release. However, Grimes *et al.* [8] construct a compelling model that emphasizes the steep

nonlinear relationship between membrane potential and transmitter release at this synapse (Figure 1C). This nonlinear relationship arises through several mechanisms, including from the steep voltage dependence of Ca^{2+} channels driving release, which only activate when depolarized above approximately –55 mV. The authors hypothesize that, when the ON cone bipolar is in a depolarized state in the dark, it sits on the linear part of this curve, and increases or decreases its vesicle release proportional to luminance increments or decrements. However, the ambient light-dependent hyperpolarization of just a few millivolts shifts the ON cone bipolar cell release to the highly nonlinear 'foot' of the activation curve (Figure 1C). In this nonlinear regime, bright objects in the visual field depolarize cone ON bipolar cells to trigger an increase in release, but dark objects that hyperpolarize do not, i.e. the ON cone bipolar cell output is rectified.

Conclusions and Future Directions

In summary, the new study by Grimes *et al*. [8] elegantly demonstrates how retinal circuit elements are effectively repurposed to execute distinct coding strategies to optimize vision under different lighting conditions. Their finding that bright light hyperpolarizes the presynaptic ON cone bipolar cell, pushing it into a nonlinear response regime, provides a simple framework to understand how subtle changes in membrane potential can lead to fundamental modifications in circuit function. In addition, their findings also raise many new questions.

Firstly, Grimes *et al.* [8] propose a model based on relatively mild changes in membrane potential of ON cone bipolar cells (3–5 mV), which is likely to be an underestimate of the true range of voltages affecting release, as their measurements were made at the soma while release occurs at the distal axon terminals. To clarify this issue, it will be necessary to determine the changes in membrane potential that AII amacrine cells impart to the cone bipolar terminal, the site of the connecting gap junctions. This may be extremely challenging and will likely require sophisticated optical imaging techniques.

Secondly, it remains to be determined what ion channels in these cells are most affected by membrane hyperpolarization. Interestingly, as Na^+ channels are expressed in the AII amacrine cells (but not in ON cone bipolar cells in the mouse), an intriguing possibility is that the network hyperpolarization brings Na^+ channels out of inactivation and thereby increases the gain of the ON cone bipolar cell synapse [17].

And thirdly, how do the changing kinetics of the ON cone bipolar output response contribute to the non-linear responses of ganglion cells [18]? A final but important question is how are the linear/non-linear properties of excitatory bipolar cells described by Grimes *et al.* [8] linked to the light-dependent changes in the inhibitory circuitry mediated by downstream amacrine cells [6]? Clearly, Grimes *et al.* [8] have defined an important path for future investigations that aim to understand the workings of complex retinal circuitry.

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[1]Department of Neuroscience, University of Pennsylvania, Philadelphia, PA 19104, USA. [2]Department of Biology, University of Victoria, Victoria, BC V8W 3N5, Canada. *E-mail: gautam@uvic.ca

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Aging: The Blurry Line between Life and Death

Although historically reactive oxygen species have been implicated as a potential cause of ageing, recent evidence suggests that a modest increase in oxidants can actually extend lifespan. A new study suggests that, in *Caenorhabditis elegans*, reactive oxygen species regulate longevity through a pathway classically linked to apoptosis.

Julia Liu and Toren Finkel*

Perhaps no organism has contributed as much to our understanding of complex biological processes as the simple roundworm, *Caenorhabditis elegans*. Investigations using this organism began in the 1970s and eventually culminated a few decades later in a detailed understanding of