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Vision: Life on the dark side

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Mice detect decreases in illumination in dim light near the visual threshold with OFF retinal ganglion cells.

Like most experimental scientists, I am a perennial optimist. Every time I suggest a new approach to my students, I overestimate the likelihood of success. I do not do this to deceive them; I truly believe that each new project will be a glorious success. My colleagues are like this too. Optimism and curiosity are the well-springs of discovery.

I think this optimistic frame of mind may explain why retinal physiologists — myself included — usually stimulate our preparations with flashes of light and almost never with flashes of darkness. Darkness seems so dreary. A little reflection should tell us, however, that we may be holding the stick by the wrong end. If we consider our friend the field mouse emerging from its den in the dim light of a new moon looking for seeds and worms, we may reflect that the greatest danger the mouse faces may come from a shadow, perhaps of an owl or hawk. What is true of a field mouse may very well have been true of early mammals scurrying about the forest floor, particularly during the nuclear winter after the fall of the massive comet or asteroid that exterminated the dinosaurs. Detecting small decreases in illumination must have been essential to their survival. We ourselves bear the mark of this

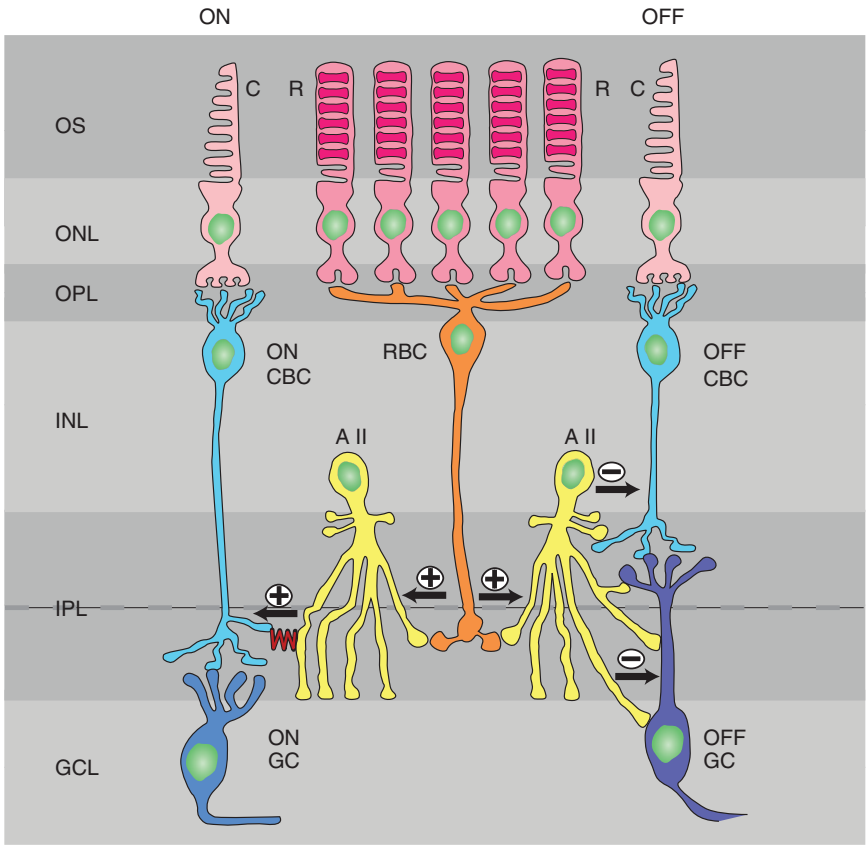

Figure 1. Processing of rod signals in the mammalian retina for dim light near the visual threshold.

Many rods synapse onto each rod bipolar cell (RBC). The RBCs then make excitatory glutamatergic synapses onto AII amacrine cells, which convey the rod signals to ON and OFF cone bipolar cells (CBCs) in the following way. The AII amacrines make gap junctions onto ON CBCs, which in turn excite ON ganglion cells (ON GCs). The AII amacrines also make glycinergic inhibitory synapses onto OFF CBCs, which convey the OFF signal to OFF GCs. AII amacrines also make direct inhibitory synapses onto the processes and somata of OFF GCs. AII, AII amacrine cell; C, cone photoreceptor; GCL, ganglion-cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; OFF CBC, off (hyperpolarizing) cone bipolar cell; OFF GC, OFF ganglion cell; ON CBC, on (depolarizing) cone bipolar cell; ON GC, ON ganglion cell; ONL, outer nuclear layer containing inner segments of rods and cones; OPL, outer plexiform layer; OS, outer segments of rods and cones; R, rod photoreceptor; RBC, rod bipolar cell. (Figure by Margery J. Fain.)

necessity: in dim background light we are about twice as sensitive to light decreases as to increases[1,2].

It is, however, the increases that have gotten all of our attention. Every physiology textbook now tells us that a rod photoreceptor can detect a single photon of light. This remarkable fact was first discovered with psychophysical (behavioral) measurements on human observers[3] and subsequently confirmed by direct recording from single rods[4]. Because the signals of rods are pooled within the retina, the threshold for vision is obtained when only a small number of rods each absorbs a single photon, probably fewer than 10 rods in a pool of many hundreds or thousands. Much is now known about how single-photon events in the photoreceptors are discriminated from noise to enable us to see the dimmest increases in illumination (see Field *et al.*[5] and Field and Sampath[6]).

But what about decreases? How do we detect a small number of 'missing' photons in the dimmest background light? Here much less is known. Enter Westö, Martyniuk and colleagues, who, as reported in this issue of *Current Biology*, have made the first direct comparison of behavior and retinal responses to what they call 'quantal shadows', or dim flashes of darkness[7]. To understand their achievement, we need to know first that the retina and — indeed — the whole of the visual system is divided into two systems called ON and OFF, which respond to increases and decreases of light. In the mammalian retina, rod and cone signals are processed by distinct ON and OFF circuits. For the cone circuit, the division into ON and OFF is produced at the first synapse from photoreceptors onto ON and OFF cone bipolar cells (Figure 1). ON cone bipolar cells depolarize to increases in illumination, and OFF cone bipolar cells depolarize to decreases. These two kinds of bipolar cells use different synaptic receptors and synapse onto ON and OFF ganglion cells. This basic division of the visual system seems to be a feature of visual processing in all vertebrates and probably arose very early in evolution in the late Cambrian[8].

For rods, the organization of ON and OFF occurs somewhat differently. Rods synapse onto a single kind of ON rod bipolar cell. There are no OFF rod bipolar cells, at least in mammals (see Wassle[9] as well as West and Cepko[10]). Rod bipolar cells make excitatory glutamatergic synapses onto a type of amacrine cell called the AII amacrine (Figure 1). AII amacrine cells make sign-preserving gap junctions onto cone ON bipolar cells and sign-reversing inhibitory (glycinergic) synapses onto cone OFF bipolar cells. The cone bipolar cells excite in turn the ON and OFF ganglion cells. As a result, the ON signal of the rod bipolar cell remains an ON signal for the ON ganglion cell but is transformed into an OFF signal for the OFF ganglion cell. In addition, AII amacrine cells can synapse directly onto OFF ganglion cells, both onto their dendrites (see, for example, Kolb and Nelson[11] and Marc *et al.*[12]) and onto their cell bodies[13]. These synapses are also glycinergic and sign-reversing. Although there are other pathways of rod signaling through a small number of direct synapses of rods onto OFF cone bipolar cells and gap junctions between rods and cones (see Fain and Sampath[14]), the pathway through the rod bipolar cells is known to be the one utilized in dim light (see, for example, DeVries and Baylor[15] and Grimes *et al.*[16]).

If we want to study how this rod retinal pathway signals responses at threshold, our approach can be straightforward for increases in illumination. We can record single-photon responses from rods and rod bipolar cells and study pooling of responses in the AII amacrine cells. For decreases, the experiments are more difficult. We cannot very well record from the rods. Quantal shadows occur in background light so dim that single-photon responses are present in only a small proportion of the photoreceptors. A decrease in the frequency of these responses in any one rod would be difficult to detect. Bipolar cells pool rod signals and are about a factor of 10 more sensitive than the rods, but even in bipolar cells the pooling wouldn't be large enough to detect responses to small decreases in illumination. Dim backgrounds *can* affect the responses of AII amacrine cells[17], but pooling is even greater in the ganglion cells, and their signals can be recorded much more easily.

But which ganglion cells? There are more than 40 different kinds in the mammalian retina (see Kerschensteiner[18]). Westö, Martyniuk and colleagues chose ON-S and OFF-S cells, which are varieties of so-called alpha cells with large dendritic fields. Although they could not be sure that these cells were the most sensitive, we can probably agree that they are among the most sensitive and a good choice to study detection in dim light. They then asked whether quantal shadows are better detected by ON-S or OFF-S cells. Either kind of cell could do the job, at least in principle. This is because both could give a maintained response to dim, steady light that could be either increased or decreased when the light intensity was diminished. When, however, Westö, Martyniuk and colleagues recorded from these two kinds of cells near the visual threshold, the answer was clear. The OFF-S cells were remarkably better and could detect light decrements down to the dimmest backgrounds tested. The ON-S cells gave too weak a response to maintained illumination to signal decreases reliably.

Westö, Martyniuk and colleagues then trained mice in a water maze. One of the arms of the maze — the one with the escape ramp — had a stimulus display consisting of a spot of decreased illumination. The mice were able to learn to distinguish the stimulus even in very dim light, at an intensity near that producing threshold responses in the OFF-S ganglion cells. Comparisons of this kind are fraught with difficulty because of the problem of calculating the amount of light entering the eye of a behaving mouse. The threshold intensities were nevertheless close, perhaps within a factor of two or three. A model combining the OFF-S responses and mouse behavior indicated that detection may be so good that it is close to the limit imposed by the Poisson distribution of light and unavoidable noise within the retina. Once again we learn that we live in the best of all possible worlds. Or at least mice do.

The work of Westö, Martyniuk and colleagues is not the end of the story. Now we need to know why OFF ganglion cells are so much better at detecting decrements. Recall (from Figure 1) that rod signals near threshold are communicated to rod bipolar cells and then down to AII amacrines. At that point the ON and OFF pathways diverge. The difference between the responses of ON-S and OFF-S ganglion cells could be the result of a difference in gain of signal transfer from AII amacrines to cone bipolar cells, which proceeds through gap junctions for one cell and glycine receptors for the other (but see Arman and Sampath[19]). The difference might also result from the direct glycinergic synapses of AII amacrines onto OFF ganglion cells[13], or from some other difference in the ON and OFF rod circuits. These and other questions will undoubtedly keep retinal physiologists busy for many years to come.

DECLARATION OF INTERESTS

The author declares no competing interests.

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