Eager Focus

ESSAYS ON APS CLASSIC PAPERS |

Making the retina approachable

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This essay looks at the historical significance of three APS classic papers that are freely available online:


OVer 50 YEARS AGO, the Journal of Neurophysiology published a paper that ranks as one of the milestones in sensory physiology: Stephen Kuffler’s (5) discovery of the center-surround receptive field of retinal ganglion cells, with antagonism between the effects of light falling on the central and surrounding portions of the field. It was immediately obvious, as Kuffler explicitly pointed out, that this receptive field organization would form the basis for spatial contrast enhancement. It was not obvious, however, how this spatial processing might arise within the retina. Sixteen years later, the Journal of Neurophysiology also published an influential pair of papers by Frank Werblin (Fig. 1) and John Dowling (Fig. 2) on the synaptic organization of the retina (3, 8), and the broad strokes of the basis for Kuffler’s (Fig. 3) findings began to take shape. (Photographs courtesy of E. Kravitz.)

The period from the mid-1960s to the mid-1970s witnessed an explosion of information about the electrophysiology of all the major cell types involved in retinal signal processing, from photoreceptors through horizontal, bipolar, and amacrine cells to the ganglion cells. A number of laboratories contributed to this explosive growth, of course, but the papers by Werblin and Dowling figured prominently. In a single classic figure (Fig. 3, Ref. 8), they provided a concise yet complete overview of the response to light stimuli at each level of retinal processing. The foundation established in these papers is still being built on: both papers received multiple citations in research publications in 2003–2004, indicating their continuing influence today.

When the Werblin and Dowling papers appeared, it had already been clear for decades that retinal ganglion cells—the output cells of the retina whose axons form the optic nerve—represent visual information in distinct ON and OFF pathways, which fire at light onset and offset, respectively. Kuffler’s (5) remarkable paper immediately focused attention on the importance of spatial factors, as well. How might the ON and OFF pathways arise within the retina? What synaptic interactions give rise to the concentric receptive fields of the ganglion cells?

Answering these questions required detailed neurophysiological analysis of the retinal neurons interposed between the receptor cells and the ganglion cells, a task that occupied retinal neurophysiologists for the next 20 years after Kuffler’s paper.

Cajal (1) had laid the anatomic groundwork for understanding the synaptic organization of the retina in the 19th century, with his extensive characterization of the cell types and the beautifully layered structure of the vertebrate retina. Given this background of detailed anatomic information, why was it so hard to move from ganglion cells to photoreceptors in the neurophysiological analysis of retinal function? In two words: action potentials. Or rather their lack. Kuffler could monitor ganglion cell activity with extracellular recordings of action potentials, but most of the other retinal neurons do not fire action potentials and rely instead on graded changes in membrane potential, as shown clearly by Werblin and Dowling (8).
Monitoring these signals requires intracellular recording, which is quite challenging in the small cells of the vertebrate retina. Graded hyperpolarizations in response to illumination—the so-called S-potentials—had been described much earlier in intracellular recordings from the retina by Svaetichin (6). However, a great deal of confusion reigned about the origin of these responses (which turned out to arise from horizontal cells) and whether they arose from neurons or glia. Indeed, because the resting potentials of retinal neurons are commonly not very negative and their light responses are small and graded, there was serious concern that the S-potentials might actually be extracellular field potentials and not intracellular recordings at all. Given this uncertainty, it is perhaps not surprising that the discovery of hyperpolarizing light responses of vertebrate photoreceptors (7) came only a few years before the Werblin and Dowling papers.

As is commonly true in neurophysiology, the selection of the experimental preparation was an important part of Werblin and Dowling’s success. Like many of their compatriots in the early days of retinal neurophysiology (and today), Werblin and Dowling turned to a cold-blooded vertebrate, the mudpuppy (Necturus maculosus), in their case, because the large neurons in these animals facilitate intracellular recording. To establish which cell class gives rise to which response type, they intracellularly stained cells with Niagara Sky Blue to mark the recording site. In similar work done contemporaneously in goldfish retina, Aki Kaneko (4) stained cells with the then new dye Procion Yellow, which had the advantage of diffusing throughout the stained cell to better reveal the complete morphology. From these papers, it was finally clear that the ON and OFF visual pathways arise in bipolar cells: OFF bipolar cells hyperpolarize to light applied in the center of their receptive field, but ON bipolar cells depolarize. The molecular basis for this separation is still under study 35 years later. It also became clear from Werblin and Dowling’s and Kaneko’s work that bipolar cells, like ganglion cells, have center-surround receptive fields, with opposing responses to illumination in the center and in the surrounding regions. Again, the underlying mechanisms are still being studied.

When John Dowling (2) published a book about the retina in 1987, he chose the title, *The Retina: An Approachable Part of the Brain*, to emphasize that the retina is fertile ground for working out the mechanisms of information processing in the central nervous system. Kuffler’s seminal publication and the Werblin and Dowling papers in the *Journal of Neurophysiology* unquestionably played a significant role in making the retina so approachable.

REFERENCES