Visual integration in the retina of the sea lamprey *Petromyzon marinus*

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ABSTRACT:
The principal effort of our research during the last three years has focused on four of the five objectives of our proposal, namely (1) characterization of the sensitivity and waveform of light responses of the principal cell types of the lamprey retina, (2) study of the synaptic physiology and pharmacology of retinal interneurons to identify mechanisms of transmitter release and identify transmitter receptor types, (3) recording of spectral properties of retinal cells to identify the flow of rod and cone information through the retina, and (4) preliminary recording from ganglion cells. We have been successful in recording from all of the major types of retinal neurons, including the photoreceptors (Morshedian and Fain, 2015, 2017; Morshedian et al., 2017), horizontal cells, bipolar cells (Ellis et al., 2020), amacrine cells, and ganglion cells. In earlier work, we have extensively characterized responses of rods and cones (Morshedian and Fain, 2015, 2017). In this contract, we have focused on the following three studies.

(1) Synaptic physiology of lamprey bipolar cells. A universal feature of the visual system in all previously studied vertebrates is the division of information into pathways specific for the onset and offset of illumination, called ON and OFF pathways. ON and OFF pathways have a central role in the detection of contrast and combine to produce complicated receptive fields in the rest of the visual system, which detect diverse aspects of the visual world. Recordings from amphibians and mammals have shown that this ON/OFF division occurs at the first synapse of the visual system between the photoreceptor cells—the rods and cones, and separate groups of ON and OFF bipolar cells. Moreover, the response in the ON bipolar cells is produced by a novel metabotropic glutamate receptor, called mGluR6, found among vertebrates only in the retina. To investigate ON and OFF pathways and bipolar-cell responses in lamprey retina, we made patch-clamp recordings from cells in retinal slices. Our experiments have

shown that lamprey retina establishes ON and OFF pathways at the level of the bipolar cells (Ellis et al., 2020). Furthermore, the ON pathway is mediated by glutamate receptors sensitive to DL-AP4 similar to the ON bipolar cells of other vertebrates, suggesting that the lamprey glutamate receptor is also mGluR6. This work shows that the fundamental division of retinal processing into ON and OFF pathways and the mechanism producing the ON bipolar-cell response first appeared in the Cambrian and have remained relatively unchanged for 500 million years.

(2) Non-image-forming perception in lamprey. Lamprey have been shown to have ganglion cells containing the visual pigment melanopsin, suggesting that lamprey have intrinsically photosensitive retinal ganglion cells (ipRGCs). These ganglion cells in other vertebrates including mammals mediate novel mechanisms of light detection now known to control several kinds of non-image-forming vision, including regulation of mood, circadian rhythm, and the pupillary light reflex (PLR). We asked whether the PLR is also present in lamprey, and whether it is controlled by melanopsin. To demonstrate a PLR in lamprey, we placed anesthetized animals in darkness on the stage of a dissecting microscope equipped with infrared image converters, and we focused down on the eyes and captured images continuously with a CCTV camera. Our experiments show that lamprey have a robust PLR, which is controlled by the pigment melanopsin as in other vertebrates but without significant input from rods and cones Morshedian et al., 2021). These experiments show that non-image-forming perception regulated by melanopsin emerged long before the radiation of present vertebrate lines and was also already present in the late Cambrian.

(3) OFF rod bipolar cells. Our previous work demonstrated that lamprey have both ON and OFF bipolar cells like other vertebrates, which seemed for the most part to receive input from both rods and cones. In mammals, rods synapse onto only a single kind of ON bipolar cell, whereas cones synapse onto both ON and OFF bipolar cells (Fain and Sampath, 2018; West and Cepko, 2021). In lower vertebrates (for example fish), most bipolar cells receive both rod and cone input and there are no pure rod bipolars (Scholes, 1975; Stell, 1978); nevertheless one cell type (called Mb) receives input predominantly from rods and seems analogous to the rod bipolars of mammals (Zimov and Yazulla, 2008). We have discovered that lamprey, in contrast to fish and amphibians, have a prominent rod bipolar cell receiving input only from rods and not cones, as in mammals; but this bipolar cell is OFF not ON. These experiments show that the organization of rod and cone inputs to bipolar cells is quite different from that in other vertebrates. Experiments are planned to characterize other bipolar cell types in the lamprey retina in more detail.