Public Oral Examination for the Degree of Doctor of Philosophy

The Ins and Outs of Melanopsin Signaling

Krystal Harrison

April 7, 2020 – 2:00 PM

https://bluejeans.com/762222261
Intrinsically photosensitive retinal ganglion cells (ipRGCs) are responsible for non-image-forming functions such as circadian photoentrainment, pupillary light reflex and the suppression of melatonin. Additionally, their axons innervate two main image-forming visual nuclei: the superior colliculus (SC) and the lateral geniculate nucleus (LGN). Furthermore, electrophysiology data discovered that ipRGCs signal to dopaminergic amacrine cells via AMPA/Kainate glutamate receptors and to displaced amacrine cells (ACs) located in the ganglion cell layer of the retina through gap junctions. Retinal ganglion cells had never been found to signal intraretinally prior to this finding.

Several labs have been exploring how ipRGCs mediate or modulate image-forming vision through their central projections and signaling to dopaminergic ACs. However, little is known about the functional roles of gap-junction signaling from ipRGCs to displaced ACs and how ipRGCs work in conjunction with rod and cone photoreceptors to mediate image-forming visual responses. Neurobiotin tracer injections, immunostaining, and optokinetic visual behavior techniques were used in this thesis to fill in this knowledge gap. Four specific aims were accomplished: 1) understand how ipRGC-coupled ACs are distributed across the retina and identify ipRGC-coupled ACs, 2) test the hypothesis that connexin36 (Cx36) couples ipRGCs to displaced ACs, 3) examine the effect of glutamatergic input on ipRGC-AC coupling, and 4) assess the effect of rods, cones and melanopsin on image-forming behavior.

Abstract

Intrinsically photosensitive retinal ganglion cells (ipRGCs) are responsible for non-image-forming functions such as circadian photoentrainment, pupillary light reflex and the suppression of melatonin. Additionally, their axons innervate two main image-forming visual nuclei: the superior colliculus (SC) and the lateral geniculate nucleus (LGN). Furthermore, electrophysiology data discovered that ipRGCs signal to dopaminergic amacrine cells via AMPA/Kainate glutamate receptors and to displaced amacrine cells (ACs) located in the ganglion cell layer of the retina through gap junctions. Retinal ganglion cells had never been found to signal intraretinally prior to this finding.

Several labs have been exploring how ipRGCs mediate or modulate image-forming vision through their central projections and signaling to dopaminergic ACs. However, little is known about the functional roles of gap-junction signaling from ipRGCs to displaced ACs and how ipRGCs work in conjunction with rod and cone photoreceptors to mediate image-forming visual responses. Neurobiotin tracer injections, immunostaining, and optokinetic visual behavior techniques were used in this thesis to fill in this knowledge gap. Four specific aims were accomplished: 1) understand how ipRGC-coupled ACs are distributed across the retina and identify ipRGC-coupled ACs, 2) test the hypothesis that connexin36 (Cx36) couples ipRGCs to displaced ACs, 3) examine the effect of glutamatergic input on ipRGC-AC coupling, and 4) assess the effect of rods, cones and melanopsin on image-forming behavior.
We found that all six ipRGC types are electrically coupled to amacrine cells, primarily via Cx36 and a few ipRGC-coupled amacrine cells are bNOS, nNOS, NPY or 5-HT immunopositive. ipRGC-AC coupling is enhanced in the presence of NMDA receptor expression in ipRGCs. We found the distribution of ipRGC-coupled amacrine cells is region specific, and rods, cones and melanopsin contribute to image-forming vision differently. Because ipRGCs remain light-sensitive in many blind patients suffering from rod and cone degeneration, a better understanding of the signaling ipRGCs could lead to novel strategies to restore sight in such patients.

Publications


Future Plans

Krystal received a full-time position with Eli Lilly and Company as a pharmaceutical sales representative in the Neuroscience Division.