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Chapter XX: POLYMODAL SENSORY INTEGRATION IN RETINAL GANGLION CELLS

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Abstract

An animal's ability to perceive the external world is conditioned by its capacity to extract and encode specific features of the visual image. The output of the vertebrate retina is not a simple representation of the 2D visual map generated by photon absorptions in the photoreceptor layer. Rather, spatial, temporal, direction selectivity and color “dimensions” of the original image are distributed in the form of parallel output channels mediated by distinct retinal ganglion cell (RGC) populations. We propose that visual information transmitted to the brain includes additional, light-independent, inputs that reflect the functional states of the retina, anterior eye and the body. These may include the local ion microenvironment, glial metabolism and systemic parameters such as intraocular pressure, temperature and immune activation which act on ion channels that are intrinsic to RGCs. We particularly focus on light-independent mechanical inputs that are associated with physical impact, cell swelling and intraocular pressure as excessive mechanical stimuli lead to the counterintuitive experience of “pressure phosphenes” and/or debilitating blinding disease such as glaucoma and diabetic retinopathy. We point at recently discovered retinal mechanosensitive ion channels as examples through which molecular physiology brings together Greek phenomenology, modern neuroscience and medicine. Thus, RGC output represents a unified picture of the embodied context within which vision takes place.

XX.1. Introduction

Life took advantage of light early on in the evolutionary process as photons were harnessed to drive the cells' energy metabolism through early photosystems and antenna complexes (Land and Nilsson, 2002). Because light is also the fastest possible way of transmitting information about the physical environment, in many, perhaps most, vertebrate species, vision emerged as a dominant sensory modality that is essential for orientation and communication with the outside world. The competitive advantages of vision sparked numerous designs of light-detecting pigments, cells and organs, culminating in the arthropod compound eye and the camera-styled eyes and layered retinas of jawed vertebrates (Gehring, 2004). The success of the vertebrate retinal design owes much to modular organization of retinal circuits and their adaptability to the demands posed by the variety of ecological niches. At each stage of visual signal transmission, information percolating through retinal

circuits appears in the form of increasingly refined aspects of the primary photoreceptor 'bitmap' that inhabit the space, time, color, direction "dimensions" of the visual stimulus (Masland, 2005). However, every level of visual processing might also be impacted by signals that are independent of light. RGCs, for example, may acquire additional inputs from circadian feedback, intraocular pressure (IOP), cardiovascular function and the immune system but may also directly respond to light (Anderson et al., 2010; Xue et al., 2011; He et al., 2012; Della Santina et al., 2013). I thus propose that vision represents an embodied sensory process that integrates information about ambient photons within the complex Gestalt of the entire body.

XX.2. Intraocular pressure, mechanical overstimulation and glaucoma

Every cell is impacted by mechanical stimuli that are inherent in tissue development and/or are contributed by its environment (Nagatomi, 2011; Tyler, 2012). The response to mechanical forces is conditioned by the types of (compressive, tensile, shear flow) forces and by (cell type-specific) molecular sensors and signaling pathways. Chronic force stimulation can compromise both function and survival of retinal tissue which is softer from tissues that surround it and consequently stretches more when exposed to mechanical strain (e.g., Križaj et al. 2014). Thus, firing properties and viability of RGCs are impacted by tensile stretch associated with elevations in IOP (Della Santina et al., 2013). If sustained, elevated IOP increases the risk of neurodegeneration and blindness due to developing glaucoma (Bonomi et al., 2001) whereas excessive swelling can compromise RGC viability in diabetic retinopathy and glaucoma (Reichenbach and Bringmann, 2010; Pinar-Sueiro et al., 2011). Because other retinal neurons appear to be less susceptible to mechanical stress, RGCs may selectively express pressure-sensitive mechanism(s) the identification of which has been one of the great challenges of contemporary vision research. Interestingly, these very mechanisms might have inspired the first known theories of vision.

XX.3. Early theories of vision are based on mechanically induced percepts of light

The phenomenological experience of visual percepts triggered by mechanical indentation of the eye may have inspired the earliest forms of human art (Lewis-Williams and Dowson, 1988) and laid the foundation for the earliest known theories of vision and physiology/medicine (Theophrast, 1917; Grüsser and Hagner, 1990; Gross, 1999; Waterfield, 2000; Yang et al., 2011). The *physiologos* (writer on nature) Alcmaeon of Croton (~450 B.C.) described the optic nerves, proposed they represented the "light-bearing paths" to the brain, identified the brain as the central sensory organ and the seat of understanding, and suggested that sensation allows humans to make reasonable judgments about the external world (*tekmairesthai*) (Celesia, 2001; Huffman, 2008). Alcmaeon was the first to report that application of physical pressure to the eye induces perception of light, and used the experience of mechanically induced visual phenomena ("pressure phosphenes") to conclude that vision is based on the transmission of light (fire) within the eye (Beare, 1917). [Phosphenes, also called "the prisoner's cinema", are also perceived by people deprived of visible light for prolonged periods of time, meditators, patients with migraine headaches and

are used to diagnose the inflamed optic nerve (optic neuritis) (Tyler, 1978). Their molecular mechanism is not understood].

As eloquently described in the review by Grüsser and Hagner (1990), another Pythagorean, Empedocles (419-430 B.C.), hypothesized that light is reflected into the eye from objects in the external world and that the eye has two channels that conduct dark and pale impressions towards the brain (i.e., phenomenological analogs of retinal ON and OFF channels). The visual extramission theory was refined by Plato (427-347 B.C.), whose theory, involving complicated interactions between external light and projected light, dominated Western views on vision well into the 18th century (Waterfield, 2000). Morgagni and Helmholtz suggested that mechanical stimulation of the eye gives rise to visual rather than other (tactile) sensations because of the hard-wired connections to the brain (Gross, 1999; Grüsser and Hagner, 1990), however the physiological mechanism that drives phosphene generation has never been elucidated. Is it possible that the mechanotransducer that subserves phosphene generation corresponds to the pressure-sensitive mechanisms that compromises the viability of RGCs in glaucoma?

XX.4. Mechanical stimuli drive RGC physiology through mechanosensitive channels

Mechanosensing ion channels can detect the effects of gravity, sound waves, muscle stretch, acceleration, shear flow, swelling and blood pressure (Kung, 2005; Tyler, 2012). Sensory stimuli transduced by some of the 28 vertebrate homologs of the *Drosophila* light-transducing TRP (transient receptor potential) channel include osmotic gradients, mechanical touch, taste, pain, temperature and certain aspects of hearing/vestibular function (Kung, 2005; Sachs, 2009; Cristensen and Corey, 2007). One isoform, TRPV4, is also the closest vertebrate homolog of *Inactive* and *Nanchung* - mechanosensitive TRPs that are essential for hearing in *Drosophila* and is expressed in mechanosensitive neurons that include cochlear hair cells, Merkel cells and sensory ganglia (Everaerts et al., 2010). Accordingly, TRPV4^{-/-} mice exhibit mechanical hyperalgesia and behavioral reduction in response to noxious mechanical stimuli and increased mechanosensory thresholds of serosal and mesenteric afferent fibers whereas gain-of-function mutations result in severe dysplasias and neuropathies (Liedtke and Friedman, 2003; Brierley et al., 2008; Loukin et al., 2010; Zimon et al., 2010). TRPV4 is important for the development of the eye (Wang et al., 2007) and is expressed in both anterior and posterior ocular tissues. Within the retina, the TRPV4 expression is confined to RGCs and glial cells (Krizaj et al., 2014). Either mechanical stimulation or exposure to TRPV4 agonists elicited >100-fold increase in RGC excitability but, when in excess, induced RGC apoptosis and astrogliosis. Consistent with the etiology of glaucoma, genetic ablation of the channel inhibited the RGC response to mechanical stimulation whereas TRPV4 overstimulation spared photoreceptors, bipolar cells and amacrine cells (Ryskamp et al., 2011; 2014). Thus, TRPV4 channels impel upon retinal output an intrinsic sensitivity to mechanical forces by acting as sensors for mechanical stress (Krizaj et al., 2014). In addition to mechanical force, TRPV4 are polymodally activated by temperature, endocannabinoids and cell swelling (Everaerts et al., 2010), suggesting that RGCs are likely to sense and respond to a wide array of thermal, chemical and mechanical

stimuli. The overall picture is complicated by the fact that the RGCs express many different types of TRP channels, which intercept different facets of the sensory world. For example, canonical TRPC6/7 channels act as transducers of light for ipRGCs (Xue et al., 2011) whereas activation of the TRPV1 nociceptor by endocannabinoids may regulate excitability and protect RGCs from mechanical stress (Jo et al., 2014; Ward et al., 2014).

XX.5. Conclusion: What is “seeing”?

In what was one the first connectomics attempts, Sidney Brenner and his colleagues in 1980s heroically reconstructed the nervous system of the nematode *Caenorhabditis elegans* with the expectation that the collage of several thousands of serial EMs will help explain the behavior of the humble worm (White et al., 1986). It turned out that the painstaking work failed to illuminate the biology of *C. elegans* behavior, which is dependent on higher-order interactions between neuronal circuits that mediate sensation, appetitive behavior, locomotion etc. Similar questions plague the modern proponents of connectomics (Seung 2012). We argue that vertebrate vision involves complex physiological operations that deconstruct the original visual map and merge light-induced signals with systemic information. In consequence, the RGC signal, which represents an integration of time-dependent primary and modulatory information, will show itself as a distorted output that is likely to frustrate attempts at computational clarity. The significance of non-visual inputs for daily visual function in diurnal vertebrates remains an exciting challenge for further research. Are they epiphenomena such as pressure phosphenes? Does mechanotransduction contribute to perception? The vertebrate retina is not a camera that translates images into 2D negatives, nor is it Adobe Photoshop that can perform a myriad filtering operations regardless of the machine that powers it. Rather, it integrates electrical/cellular signals induced by the absorption of photons with a myriad of intrinsic cellular processes that reflect the circadian, metabolic, age-dependent etc. state of the organism. Therefore, seeing in its phenomenological sense cannot be considered independently of the organism's environment, individual and social context because the perceiver's access to visual data streams depends on specific context-dependent circumstances that may include the time of day and bodily state. Perhaps we should view vision as an emergent process that rapidly defeats simplistic quests for mathematic tractability - one that is possessed of an intrinsic sensitivity to the present moment inhabited by the entire organism.

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