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Distinct subcomponents of mouse retinal ganglion cell receptive fields are differentially altered by light adaptation

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ABSTRACT

The remarkable dynamic range of vision is facilitated by adaptation of retinal sensitivity to ambient lighting conditions. An important mechanism of sensitivity adaptation is control of the spatial and temporal window over which light is integrated. The retina accomplishes this by switching between parallel synaptic pathways with differing kinetics and degrees of synaptic convergence. However, the relative shifts in spatial and temporal integration are not well understood – particularly in the context of the antagonistic spatial surround. Here, we resolve these issues by characterizing the adaptation-induced changes to spatiotemporal integration in the linear receptive field center and surround of mouse retinal ganglion cells. While most ganglion cells lose their antagonistic spatial surround under scotopic conditions, a strong surround is maintained in a subset. We then applied a novel technique that allowed us to analyze the receptive field as a triphasic temporal filter in the center and a biphasic filter in the surround. The temporal tuning of the surround was relatively maintained across adaptation conditions compared to the center, which greatly increased its temporal integration. Though all phases of the center's triphasic temporal response slowed, some shifted significantly less. Additionally, adaptation differentially shifted ON and OFF pathway temporal tuning, reducing their asymmetry under scotopic conditions. Finally, spatial integration was significantly increased by dark adaptation in some cells while it decreased it in others. These findings provide novel insight into how adaptation adjusts visual information processing by altering fundamental properties of ganglion cell receptive fields, such as center-surround antagonism and space-time integration.

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1. Introduction

With a photoreceptor population composed of 97% rods (Jeon, Strettoi, & Masland, 1998), mice have particularly well-developed dim light (scotopic) vision. In addition, their bright light (photopic) vision is comparable to primates by many measures, including light sensitivity (Naarendorp et al., 2010) and temporal tuning (Wang, Weick, & Demb, 2011). In combination with the conserved structure of their rod and cone pathways relative to other mammals, these factors make mice a useful model for studying mechanisms of light adaptation, including pupillary reflexes (Pennesi, Lyubarsky, & Pugh, 1998), the relative sensitivity of rod/cone pathways (Abd-El-Barr et al., 2009), and various synaptic nonlinearities involved in rod pathways (Chang & He, 2014; Field & Rieke, 2002; Jarsky et al., 2011).

Across light adaptation states, retinal neurons maintain a dynamic balance between sensitivity and spatiotemporal acuity. In dark conditions, for example, their light sensitivity is increased in part by expanding the spatial collecting area and lengthening the temporal collecting window (Barlow, Fitzhugh, & Kuffler, 1957; Enroth-Cugell & Shapley, 1973; Pandarinath, Victor, & Nirenberg, 2010; Pandarinath et al., 2010). Broadening spatiotemporal integration in this fashion increases both the number of photons detected and the uncertainty about where and when they occurred. Retinal neurons therefore gain light sensitivity by sacrificing spatiotemporal acuity. Here, we utilize mice to characterize the alterations in spatiotemporal integration induced by light adaptation at the level of the retinal output neurons, ganglion cells (RGC).

Previous studies of dark adaptation in mouse RGCs observed significant or complete loss of the antagonistic surround (Barlow et al., 1957; Tikidji-Hamburyan et al., 2015) and broadening in

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both temporal (Pandarinath, Bomash, et al., 2010; Pandarinath et al., 2010; Wang et al., 2011) and spatial integration (Dedek et al., 2008). However, because the antagonistic surround has proven difficult to detect even under photopic conditions (Cang et al., 2005; Della Santina, Inman, Lupien, Horner, & Wong, 2013), the possibility exists that it may have been missed in a subset of cells. In addition, changes in spatial and temporal filtering have typically been studied separately from each other and characterized by one or two filters. This approach, though simplifying, has several risks, including the misattribution of shifts in spatial tuning to temporal sources and vice versa.

In this report we use a new technique to study receptive field subcomponents with distinct spatiotemporal filtering. This allows us to isolate and compare light adaptation's effect on the antagonistic spatial surround and the receptive field center. In addition, we explore how adaptation impacts the ON and OFF retinal pathways. These features – center-surround antagonism, parallel rod and cone pathways, and parallel ON and OFF pathways – are critical for visual function from the retina to visual cortex. By applying our unique space-time model to study large populations of RGCs under both lighting conditions, we gain new insights into how their interactions shape visual processing.

2. Methods

2.1. Ethical approval

Mice were cared for and handled following approved protocols from the Animal Care and Use Committee of Baylor College of Medicine and in compliance with the National Institutes of Health guidelines for the care and use of experimental animals. All mice were euthanized by cervical dislocation after anesthetizing with isoflurane.

2.2. Multielectrode recording

C57BL/6J mice were kept on a regular light/dark cycle and experiments were performed diurnally at 3 to 4 months of age. Mice were dark adapted for at least 90 min prior to euthanasia. Eyes were removed under infrared illumination using night vision (Nitemare, BE Meyers, Oregon) and retinas were dissected in a dish containing carboxygenated recording solution. Retinas were placed RGC side up onto cellulose filter paper (0.45 μm HA, Millipore) and transferred onto an electrode array. The preparation was retained with a plastic ring.

The retina was kept at 35.6 °C and perfused at 2 mL/min with pre-warmed and carboxygenated (95% O_2, 5% CO_2) recording medium (in mM: NaCl, 124; KCl, 2.5; $CaCl_2$, 2; $MgCl_2$, 2; NaH_2PO_4, 1.25; $NaHCO_3$, 26; and glucose, 22) at pH 7.35 (Tian and Copenhagen, 2003). The multielectrode array (MEA-60, Multichannel Systems, Tübingen Germany) had 60 electrodes spaced 100 μm apart, each with a diameter of 10 μm. RGC action potentials were recorded at 20 kHz and pre-filtered with a 0.1 Hz high-pass hardware filter.

2.3. Light calibration

Similar to our previous report (Cowan, Sabharwal, & Wu, 2016) and those of others (Pandarinath et al., 2010), the ambient light level during an experiment was measured as wavelength specific irradiance ($E(\lambda)$, in microwatts cm^{-2}) in the plane of the preparation (Thor Labs, S170C and Edmund Optics, SpectraRad). Photon flux in photoisomerizations/photoreceptor/second (Φ) was calculated as shown in Eq. (1).

$$\Phi = a_c(\lambda_{max}) \sum_{\lambda} N_p(\lambda)\tau(\lambda)S_r(\lambda). \quad (1)$$

where $a_c(\lambda_{max})$ is the effective collecting area of a photoreceptor at its peak wavelength (0.34 μm^2 for cones and 0.67 μm^2 for rods) (Lyubarsky, Daniele, & Pugh, 2004; Pandarinath, Bomash et al., 2010; Pandarinath et al., 2010), $N_p(\lambda)$ is the photon flux per second, and $\tau(\lambda)$ is wavelength-dependent transmissivity of the neural retinal (Alpern, Fulton, & Baker, 1987). Finally, $S_r(\lambda)$ is sensitivity relative to the peak intensity which encompasses the wavelength dependence of both quantum efficiency and molar absorbance coefficients. The ambient photopic light level stimulated rods at 757.9 R*/sec, M-cones at 384.6 R*/sec, and S-cones at 8.0 R*/sec. Neutral density filters were used to create three log unit attenuation, creating an ambient scotopic light level that stimulated rods at 0.8 R*/sec, M-cones at 0.4 R*/sec, and S-cones at 0.008 R*/sec.

2.4. White noise receptive field measurements

Receptive fields were mapped using random binary white noise checkerboards presented at 15 Hz from an optically reduced image from a computer monitor (Dell, SXGA-JF311-5100) for up to 1.5 h. Each square in the checkerboard was either black or white and 50 μm on a side. The stimulus was created and presented with PsychToolbox (Brainard, 1997; Pelli, 1997).

2.5. Spatial pooling and temporal characterization

The receptive field was first fit by combining a single two-dimensional Gaussian with a biphasic temporal filter. This spatiotemporal fit of the receptive field was used to divide the spatial inputs into nine annular regions, each spanning one standard deviation of radial distance. Temporal STAs within these annuli were summed and divided by the square root of the number of inputs to normalizes their noise levels. These were used to generate the space-time maps shown in Fig. 2. For surround characterization the annular STAs were summed.

2.6. The Sum of Separable Subfilters (SoSS) model

The SoSS model is described in our previous report (Cowan et al., 2016), but in brief it models the receptive field as the sum of up to five subfilters. We determined the number of subfilters necessary by first performing a model fit independently for each temporal trace across space for all cells. All subfilters fell into one of five clusters based on their polarity and temporal properties. The SoSS model characterizes each cell by combining these five subfilters, each with a unique spatial filter. An example of a 2 subfilter model is shown in Fig. 1B. Each subfilter, $w_i(x,y,t)$ is the product of a low-pass filter impulse response, $f_i(t)$, and a two-dimensional spatial Gaussian, $g_i(x,y)$:

$$f_i(t) = \frac{p_i * \left(\frac{t}{\tau_i}\right)^{n_i} * e^{-n_i * \left(\frac{t}{\tau_i} - 1\right)}}{e^{-n_i - 1}} \quad (2)$$

$$g_i(x,y) = k_1 e^{a(x-c_x)^2 + 2b(x-c_x)(y-c_y) + c(y-c_y)^2} \quad (3)$$

The τ and n in Eq. (2) represent the time constant and filter order. Both interact to shape the temporal profile. All subfilters for a cell had the same spatial center and rotation, and their polarities were constrained based on the peak amplitude of the STA. We performed a weighted least squares regression on the annular-averaged data, where the weights were the square root of the number of spatial inputs in each annulus.