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Expected and Unexpected Properties of Melanopsin Signaling

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Since its discovery by Provencio et al. (1998), the structural and functional homologies of melanopsin with the rhabdomic class of invertebrate photopigments have been progressively confirmed. Rhabdomic photopigments possess the property of bistability and can thereby use light to drive both photosensory (bleaching) and photoisomerase (recovery) functions, in strong contrast to the rods and cones of vertebrates, which rely on light-independent mechanisms in other cells for regeneration of the chromophore. In 2005, studies in cells that heterologously express melanopsin (Melyan et al., 2005; Panda et al., 2005; Koyanagi et al., 2005) provided strong evidence that melanopsin too displays bistability.

To ask whether bistability in vitro carries over to in vivo physiological responses, we tested whether prior stimulation with appropriate wavelengths restores or increases circadian responsiveness compared with a previous, identical light exposure (Mure et al., 2007). Our results were consistent with the prediction that, for bistable photopigments, the relative proportions of melanopsin in the R and M states (*11-cis* and *all-trans-retinal* bound forms, respectively) can be manipulated by prior adapting lights. In addition to defining the spectral, irradiance, and duration dependence of the response, we showed that mice that lack melanopsin retain the phasic components originating from rods and cones (Drouyer et al., 2007) but not light enhancement of the response.

The interpretation that these results reflect the bistable nature of the melanopsin photopigment appear to be challenged by Mawad and Van Gelder (2008), who failed to detect any photopotential in postnatal retinas following previous exposure to long wavelength light. Mawad and Van Gelder propose several possible explanations for this discrepancy, including interactions of rod and cone inputs with melanopsin intrinsically photosensitive retinal ganglion cell (ipRGC) physiology, differences related to developmental factors (postnatal versus adult), and differences between their in vitro conditions and local in vivo environment. They also suggest that our observed augmentation due to long wavelength light occurs downstream of the retinal ipRGC action potential, as suggested in their previous study (Zhu et al., 2007). We suggest that another possible source of the discrepant findings could be the use of short wavelength (480 nm) test and reference lights of 10^{14} photons/cm²/sec by Mawad and Van Gelder, which was previously shown to cause saturation of the response in both neonatal and adult retinas (Tu et al., 2005). In general, it is difficult to drive a response higher than saturation in either a bistable or ciliary photopigment system. In our study in the mouse it was essential to use irradiance values that elicited a 50% saturating value for each type of response to measure either increases or decreases in amplitude. This is consistent with the "small but statistically significant enhancement" observed by Mawad and Van Gelder (their

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Figure 5) at lower irradiances. It is also puzzling that, despite the high irradiances used, many cells did not show sustained responses to light and none displayed a poststimulus persistent response, whereas in a previous study all ipRGCs showed robust and persistent responses (Tu et al., 2005). The robust sustained and persistent responses (similar to the invertebrate prolonged depolarization afterpotential response) are hallmarks of the melanopsin ipRGC phenotype (Berson et al., 2002; Dacey et al., 2005).

Mawad and Van Gelder's conclusions from their failure to find photopotential in ipRGCs recorded in vitro are primarily discordant with those of previous in vitro studies using heterologous expression of melanopsin (Melyan et al., 2005; Panda et al., 2005; Koyanagi et al., 2005) rather than with previous in vivo results. A previous study from the Seattle group (Zhu et al., 2007) is in agreement with ours (Mure et al., 2007) in concluding that light can, under appropriate conditions, enhance (or photopotential) pupil constriction and that this response is melanopsin dependent (although they disagree as to its basis in melanopsin bistability, suggesting instead a downstream effect). In our view, the most parsimonious explanation, which can account for the broadest range of relevant results, although requiring further confirmation, is simply that melanopsin bistability has functional consequences both in vitro and in vivo.

REFERENCES

- Berson DM, Dunn FA, and Takao M (2002) Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 295:1070-1073.
- Dacey DM, Liao HW, Peterson BB, Robinson FR, Smith VC, Pokorny J, Yau KW, and Gamlin PD (2005) Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. *Nature* 433:749-754.
- Drouyer E, Rieux C, Hut RA, and Cooper HM (2007) Responses of suprachiasmatic nucleus neurons to light and dark adaptation: Relative contributions of melanopsin and rod-cone inputs. *J Neurosci* 27: 9623-9631.
- Koyanagi M, Kubokawa K, Tsukamoto H, Shichida Y, and Terakita A (2005) Cephalochordate melanopsin: evolutionary linkage between invertebrate visual cells and vertebrate photosensitive retinal ganglion cells. *Curr Biol* 15:1065-1069.
- Mawad K and Van Gelder RN (2008) Absence of long-wavelength photic potentiation of murine intrinsically photosensitive retinal ganglion cell firing in vitro. *J Biol Rhythms* 23:387-391.
- Melyan Z, Tarttelin EE, Bellingham J, Lucas RJ, and Hankins MW (2005) Addition of human melanopsin renders mammalian cells photoresponsive. *Nature* 433:741-745.
- Mure LS, Rieux C, Hattar S, and Cooper HM (2007) Melanopsin-dependent nonvisual responses: evidence for photopigment bistability in vivo. *J Biol Rhythms* 22:411-424.
- Panda S, Nayak SK, Campo B, Walker JR, Hogenesch JB, and Jegla T (2005) Illumination of the melanopsin signaling pathway. *Science* 307:600-604.
- Provencio I, Jiang G, De Grip WJ, Hayes WP, and Rollag MD (1998) Melanopsin: An opsin in melanosomes, brain, and eye. *Proc Natl Acad Sci U S A* 95:340-345.
- Tu DC, Zhang D, Demas J, Slutsky EB, Provencio I, Holy TE, and Van Gelder RN (2005) Physiologic diversity and development of intrinsically photosensitive retinal ganglion cells. *Neuron* 48:987-999.
- Zhu Y, Tu DC, Denner D, Shane T, Fitzgerald CM, and Van Gelder RN (2007) Melanopsin-dependent persistence and photopotential of murine pupillary light responses. *Invest Ophthalmol Vis Sci* 48:1268-1275.