Photoreceptors in health and monogenic disease: from half a billion years ago to the future

Omar A. Mahroo[1-4]

Emma Duignan[5]

1. Institute of Ophthalmology, University College London, Bath Street, London, UK
2. Retinal and Genetics Services, Moorfields Eye Hospital, 162 City Road, London, UK
3. Section of Ophthalmology, King's College London, St Thomas' Hospital Campus, Westminster Bridge Road, London, UK
4. Physiology, Development and Neuroscience, University of Cambridge, Downing Street, Cambridge, UK
5. Royal Victoria Eye and Ear Hospital, Adelaide Road, Dublin, Ireland

Correspondence to Omar Mahroo at address 1 above. Email: o.mahroo@ucl.ac.uk

ORCID: 0000-0003-1254-0832

Running title: Photoreceptors in health and monogenic disease

Keywords: Retina, Rod photoreceptors, Cone photoreceptors, Electroretinography, Dark adaptation, Optogenetics

Rod and cone photoreceptors are highly specialised cells, with unique structural modifications to subserve their function as adaptive light detectors and the first neurons in the visual pathway. Monogenic diseases of the retina are amongst the largest causes of blindness certification in children and working age adults in many countries. The majority of these diseases result from perturbations of photoreceptor structure or function. Recent transformational developments in the field include improvements in understanding the molecular basis of phototransduction, photoreceptor physiology and pathophysiology, advances in non-invasive evaluation of photoreceptor structure and function in the living human eye (in health and disease), accelerating developments in genomic sequencing techniques enabling genetic diagnosis in increasing numbers of individuals with inherited retinal disease, and, for the first time, the demonstration of efficacy of some novel therapies in selected patients with these hitherto untreatable conditions.

A symposium entitled “Photoreceptors in health and monogenic disease: advances in understanding physiology and treating pathophysiology” was held at annual conference of the Physiological Society in 2021. This editorial introduces, with context, the ensuing reviews (Lamb, 2022; Jiang & Mahroo, 2022; De Silva & Moore, 2022) authored by the symposium speakers and published in this special issue.

Molecular basis of phototransduction

Phototransduction, the process by which the detection of light by the photoreceptor brings about an electrical response, has been elucidated at the molecular level in rods and cones, with important differences between the two classes of photoreceptor characterised. (Intrinsically photosensitive ganglion cells are a more recently described class of photoreceptor, serving numerous functions, but whose direct role, if any, in image-forming vision is less clear.) Lamb (2022) reviews current knowledge of rod and cone phototransduction, including discussion of the proteins involved, mathematical consideration of the kinetics of phototransduction activation and inactivation, as well as an outline of evolutionary history of the relevant proteins, tracing developments back to the two rounds of whole genome duplication over 500 million years ago.

Most of the genes encoding the proteins of phototransduction, and discussed by Lamb (2022), have also been implicated in monogenic retinal diseases (relevant to the review by De Silva and Moore (2022) in this issue). Pathogenic variants in *RHO* (encoding rhodopsin), *GNAT1* (encoding the alpha

subunit of the rod G-protein transducin), *PDE6A* and *PDE6B* (encoding subunits of rod phosphodiesterase), and *CNGA1* and *CNGB1* (encoding subunits of the rod cyclic nucleotide gated cation channel) have all been associated with retinitis pigmentosa. Variants in genes encoding equivalent proteins in cone phototransduction (the cone opsin genes, *GNAT2*, *PDE6C*, *PDE6H*, *CNGA3* and *CNGB3*) are associated with cone dysfunction disorders (including achromatopsia). Genes encoding proteins involved in recovery of the light response (including *GRK1*, *SAG*, *RGS9*) and with calcium feedback pathways (*GUCY2D*, *GUCA1A*, *SLC24A1*) are also associated with types of inherited retinal disease.

Evaluating retinal function *in vivo* and tracking adaptation

Advances in retinal imaging have allowed evaluation of retinal structure with unprecedented resolution. Adaptive optics affords *in vivo* imaging of single photoreceptors. Optical coherence tomography, whose use is widespread in clinical settings, yields a cross-sectional image of the retinal layers within seconds. The electroretinogram (ERG) represents the electrical response of the retina to light and has been recorded in human subjects for over a century. In recent decades, techniques have been standardised in clinical practice to enable a global evaluation of rod-driven and cone-driven signals. Other techniques (pattern ERG, multifocal ERG) permit evaluation of neuronal function in more localised areas of the retina. The mathematical models of phototransduction activation reviewed by Lamb (2022) have also been applied to ERG recordings to derive parameters reflecting kinetics of phototransduction in rods and cones.

The ability of the visual system to adapt permits maintenance of sensitivity over several orders of magnitude of background intensities. Whilst some of this adaptation is post-receptoral, and some reflects a switch from rod to cone-mediated vision as ambient intensities increase, a large contribution comes from changes in kinetics of the light response within the photoreceptors themselves. Light adaptation is rapid, occurring within seconds following changes in ambient intensity, but dark adaptation, the regaining of sensitivity following substantial photopigment bleaching, takes tens of minutes. A key limiting factor is delivery of chromophore (11-*cis*-retinal) to photoreceptor outer segments via the retinoid cycle. In some monogenic disorders, including those involving genes encoding proteins involved in the retinoid cycle and proteins involved in shut-off of phototransduction, dark adaptation can be substantially delayed.

In clinical practice, standard ERG tests are deployed to probe retinal function in two adaptive states: fully dark-adapted (following 20 min of dark adaptation) or light-adapted to a single light background. The kinetics of light and dark adaptation are not routinely measured; dark adaptation is more commonly assessed psychophysically. In their review, Jiang and Mahroo (2022) discuss use of the ERG to track dynamically dark adaptation of rod-driven and cone-driven signals following bleaching exposures, and the insights into cellular mechanisms (including retinoid cycle kinetics) gained from such studies, as well as potential utility of such techniques in the context of clinical disorders, including several monogenic diseases.

Optogenetics as a therapeutic approach in inherited retinal disease

The absence of effective therapeutic interventions in the vast majority of inherited retinal diseases (including those associated with the genes discussed above) is frustrating. Gene-replacement strategies have been explored for some time, and the development of a licensed treatment for one monogenic disease (associated with bi-allelic pathogenic variants in the *RPE65* gene, which encodes a protein involved in the retinoid cycle) has been a major step forward. Other techniques being explored include optogenetics, reviewed by De Silva and Moore (2022).

In most inherited retinal degenerations, there is progressive loss of photoreceptors, whilst the inner layers of the retina typically remain intact. These include bipolar cells and ganglion cells (the axons of the latter forming the output channels of the retina and projecting to the brain). Optogenetic therapies aim to confer light sensitivity (photoreception) to these cells by engendering expression of light-sensitive proteins, with the objective of restoring some level of vision. Such proteins include ion channels, ion pumps and G-protein coupled receptors, including melanopsin (the native opsin in intrinsically photosensitive ganglion cells). Potential advantages, if such an approach were to be successful, include applicability to a wide range of inherited dystrophies (irrespective of the particular genetic cause) and a wider therapeutic window of more advanced stages of disease (after widespread photoreceptor death) than would be amenable to targeted gene replacement strategies.

Conclusions

The complementary symposium reviews highlight the many synergistic developments in our understanding that are occurring in parallel. The elucidation of “natural” phototransduction and

detailed physiology of rod and cone photoreceptors has helped in understanding mechanisms of disease and in paving the way for therapeutic strategies, including the “artificial” induction of phototransduction in non-naturally photoreceptive cells. More precise methods of structural and functional assessment of photoreceptors *in vivo* have yielded insights into physiology and pathophysiology as well as providing techniques for objectively evaluating efficacy of novel therapies. The challenges that remain are numerous and significant. It is hoped that this series of reviews, though only concentrating on a few specific themes, contributes to a better understanding of the field, and might help guide the framing of future investigations.

References

De Silva SR & Moore AT (2022). Optogenetic approaches to therapy for inherited retinal degenerations. *J Physiol.* 2022 Jul 31. doi: 10.1113/JP282076. Epub ahead of print. PMID: 35908243.

Jiang X & Mahroo OA (2022). Human retinal dark adaptation tracked in vivo with the electroretinogram: insights into processes underlying recovery of cone- and rod-mediated vision. *J Physiol*. 2022 May 25. doi: 10.1113/JP283105. Epub ahead of print. PMID: 35612091.

Lamb TD (2022). Photoreceptor physiology and evolution: cellular and molecular basis of rod and cone phototransduction. *J Physiol*. 2022 Apr 12. doi: 10.1113/JP282058. Epub ahead of print. PMID: 35412676.

Additional information

Competing Interests: The authors have no competing interests.

Funding: OAM receives funding from the Wellcome Trust (206619/Z/17/Z) and Moorfields Eye Charity. Views expressed are those of the authors and not the funding organisations.