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Review

Lipid signaling in *Drosophila* photoreceptors ☆

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ABSTRACT

Drosophila photoreceptors are sensory neurons whose primary function is the transduction of photons into an electrical signal for forward transmission to the brain. Photoreceptors are polarized cells whose apical domain is organized into finger like projections of plasma membrane, microvilli that contain the molecular machinery required for sensory transduction. The development of this apical domain requires intense polarized membrane transport during development and it is maintained by post developmental membrane turnover. Sensory transduction in these cells involves a high rate of G-protein coupled phosphatidylinositol 4,5 bisphosphate [$PI(4,5)P_2$] hydrolysis ending with the activation of ion channels that are members of the TRP superfamily. Defects in this lipid-signaling cascade often result in retinal degeneration, which is a consequence of the loss of apical membrane homeostasis. In this review we discuss the various membrane transport challenges of photoreceptors and their regulation by ongoing lipid signaling cascades in these cells. This article is part of a Special Issue entitled Lipids and Vesicular Transport.

1. Introduction

Photoreceptors are primary sensory neurons that are able to detect light and transduce it into an electrical signal. Given their primary role in detecting photons, photoreceptors need to organize their structure to maximize the probability of photon absorption. In order to achieve this goal, photoreceptors usually expand and dedicate a proportion of their plasma membrane into a region that is light sensitive. Based on the morphology of this light-sensitive membrane, metazoan photoreceptors are grouped into two classes namely ciliary and microvillar [1,2]. In ciliary photoreceptors the photosensitive membranes are generated from a modified primary cilium. By contrast, in microvillar photoreceptors the light sensitive membrane is generated by folding of the apical domain of a polarized cell into tiny finger like projections called microvilli. Although it was originally proposed that ciliary and microvillar photoreceptors constitute classes that are present in distinct animal groups, we now know that both types are present in nearly every phylum in the animal kingdom.

Functionally ciliary photoreceptors (eg: vertebrate rods) respond to photon absorption with a hyperpolarizing electrical signal; by contrast microvillar photoreceptors (eg: insect photoreceptors) respond to light with a depolarizing electrical response. However this distinction too is not absolute as there are examples of photoreceptors such as the parietal eye of the lizard that are ciliary in structure but harbor both a hyperpolarizing as well as depolarizing response to light [3].

Regardless of their structural organization, photoreceptors face a number of challenges with respect to organizing their structure and function in order to deliver optimal physiological output. Lipid signaling plays a number of distinct functional roles in these processes. In this review, we discuss these issues in the context of *Drosophila* photoreceptors.

2. Structure and development of *Drosophila* photoreceptors

Insects have a compound eye that is composed of regular repeating structural units called ommatidia. In *Drosophila* that we will discuss in detail, each eye consists of approximately 750 ommatidia. Each ommatidium is a precise nineteen cell assembly composed of eight photoreceptors and eleven accessory cells. Each photoreceptor is a large (ca. 50 μm long growing to a 100 μm in a 7 day old fly [4]) polarized cell (Fig. 1A). The apical domain of each photoreceptor is folded into a variable but large number (ca. $4*10^4$, although this number varies enormously) of microvilli that are 1–2 μm long and 0.05 μm in diameter. Together the microvilli of a single photoreceptor form a rod shaped structure referred to as a rhabdomere (Fig. 1C). Estimates from electrophysiological measurements (capacitance) [5] as well as geometrical calculations [4] estimate the surface area of a single photoreceptor to be ca. $1*10^4$ μm^2. Microvillar membrane is thought to constitute ca. 90% of the plasma membrane of the photoreceptor.

Insect photoreceptors are developed from primordial larval structures called the eye imaginal disc. This disc consists of a single layer of epithelial cells. Following three rounds of mitosis and a number of cell specification events this epithelial monolayer undergoes morphological changes that result in its transformation into the three dimensional structure of the adult retina which in a newly eclosed fly is around

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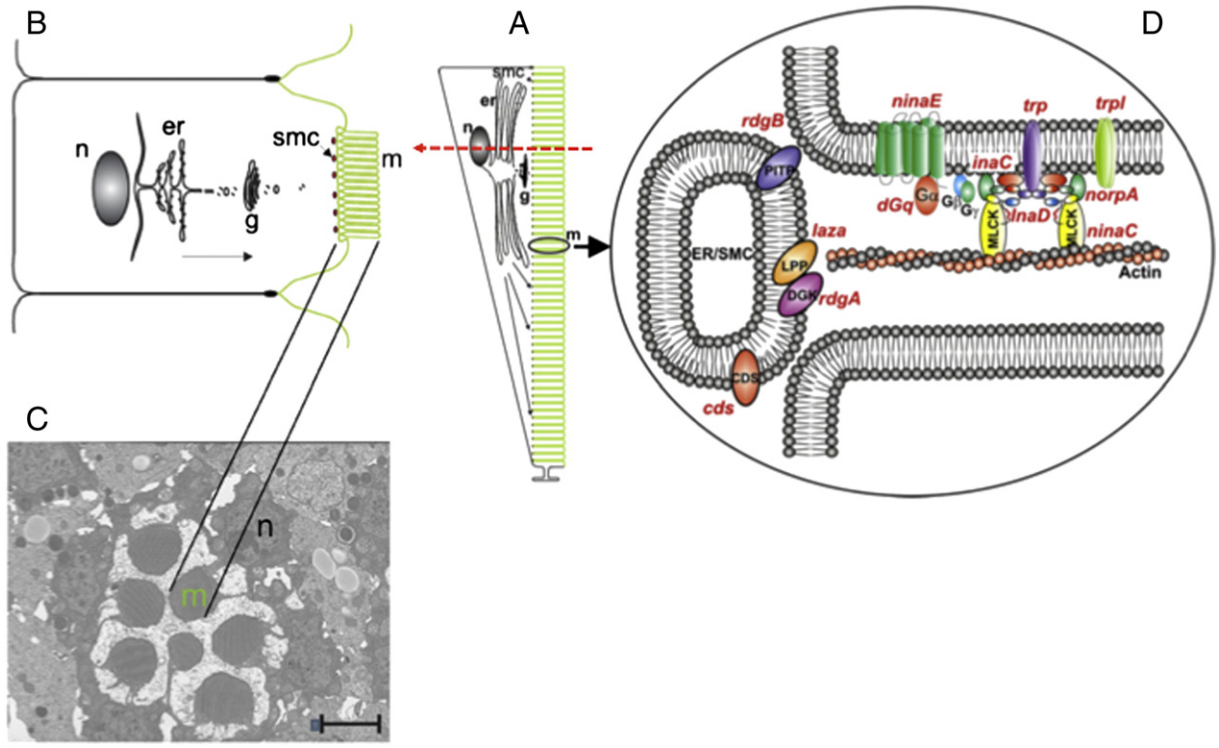

Fig. 1. *Drosophila* photoreceptor structure. (A) Longitudinal section through a single photoreceptor showing the relationship of the cell body and rhabdomeres composed of microvilli (m). Organelles located in the cellbody are shown. The submicrovillar cisternae (smc) are shown at the junction of the cell body and the rhabdomere. The rhabdomeral plasma membrane is shown in green. The red dotted line shows the level of the cross section in B. n, nucleus; g, Golgi; er, endoplasmic reticulum. (B) Cross section through a photoreceptor at the level of the nucleus showing the organelles. The arrow marks the direction of polarized transport to the apical domain. (C) A representative TEM from a wild-type ommatidium is shown with the microvilli and nucleus marked. Bar, 2 μm. (D) Expanded view of a microvillus and associated SMC. The localization of known transduction components is shown. Mutants in each component where available are shown in italics. Transduction components and mutants in these are described in the text. PITP-phosphatidylinositol transfer protein; LPP-lipid phosphate phosphohydrolase; DGK-diacylglycerol kinase; CDS-Cytidine diphosphate diacylglycerol synthase; MLCK-myosin light chain kinase; Gα, Gβ and Gγ are the α, β and γ subunit of the heterotrimeric G-protein.

50 μm thick. Thus during development, the precursor cells of the *Drosophila* eye undergo a substantial increase in size which requires generating new membrane [4]. Indeed during the last 30% of pupal development, photoreceptors show an approximately fourfold increase in plasma membrane surface area [6] a process that requires a massive surge in polarized membrane transport capacity starting at ca. 70% p.d (pupal development).

3. Biochemical strategies of transduction

Regardless of structural organization of photoreceptor membranes, the light-sensitive membranes of photoreceptors are packed with a visual pigment composed of a vitamin A based chromophore and a seven transmembrane helix apoprotein, opsin. Opsins belong to two broad groups: c-opsins (c for ciliary) and r-opsins (r for rhabdomeric); this classification is based both on molecular phylogeny and also on the cell types in which these proteins are expressed [7]. A unifying feature of phototransduction in both ciliary and microvillar photoreceptors is that the absorption of light by rhodopsin results in its photoisomerization into an active form. The principle outcome of this event is the activation of the α-subunit of a heterotrimeric G-protein complex. The subsequent events of transduction are very different between vertebrate-ciliary and microvillar photoreceptors. In most ciliary photoreceptors, the α-subunit of the G-protein that is activated is transducin (G_t). G_t in turn activates a phosphodiesterase (PDE) that hydrolyzes cyclic GMP (cGMP). In the dark, levels of photoreceptor cGMP are high, maintaining the cGMP-gated channels in an open state. Light induced PDE activity results in a drop in cGMP concentration, shutting these channels and resulting in hyperpolarization of the photoreceptors. The molecular processes underlying these events have been worked out in great detail and are reviewed in [8].

By contrast, microvillar photoreceptors that dominate in arthropods and insects appear to use the G-protein subunit Gq which in turn activates phospholipase C (PLC) ultimately leading to the depolarization of the cell. However there appears to be some dichotomy in the events subsequent to PLC activation; while inositol 1, 4, 5 trisphosphate ($InsP_3$) induced Ca^{2+} release appears to be required for activation in some species (eg: *Limulus*, honeybee), in others such as Dipteran flies $InsP_3$ induced Ca^{2+} release does not appear to play a role and the lipid products of PLCβ activity have been implicated in activation. Thus lipid signals play a key role as messengers in these cells and under the conditions of bright light illumination they show high rate of lipid turnover.

Functionally microvillar photoreceptors are characterized by their ability to generate quantum bumps with high sensitivity and amplification during dim light illumination. This in part has been attributed to the high degree of compartmentalization afforded by the confines of individual microvillus that allows the products of transduction (such as Ca^{2+}) to reach high concentrations [9]. In addition, microvillar photoreceptors can continue to respond under conditions of very bright illumination. This has been attributed to the ability of individual microvilli to detect and respond to photons of light. By contrast vertebrates have resolved the problem of dynamic range by having two kinds of photoreceptors namely rods and cones; rods respond with high sensitivity to low light while cones get engaged only in bright light.

4. Biochemistry of lipids in photoreceptors

Many previous studies have addressed the lipid composition of *Drosophila* membranes. Unlike mammalian cells where the major glycerophospholipid is phosphatidylcholine (PC), *Drosophila* membranes