Review

Drosophila visual transduction

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Visual transduction in the *Drosophila* compound eye functions through a pathway that couples rhodopsin to phospholipase C (PLC) and the opening of transient receptor potential (TRP) channels. This cascade differs from phototransduction in mammalian rods and cones, but is remarkably similar to signaling in mammalian intrinsically photosensitive retinal ganglion cells (ipRGCs). In this review, I focus on recent advances in the fly visual system, including the discovery of a visual cycle and insights into the machinery and mechanisms involved in generating a light response in photoreceptor cells.

Introduction

Drosophila phototransduction has been scrutinized for more than 40 years, and provides a genetic paradigm for signaling cascades that employ phosphoinositides and TRP channels [1–4]. During the past decade, it has become clear that there exists a new class of photoreceptor cells in mammals, referred to as ipRGCs [5], which function through a signaling cascade akin to fly visual transduction [6–9]. The ipRGCs contribute primarily to photoentrainment of circadian rhythm, pupillary constriction and sleep [10–15]. In this review, I focus on recent advances in understanding the fly visual system. Such findings include the discovery of a visual cycle, insights into the mechanism activating the TRP channels, the demonstration of dynamic interactions with the inactivation but no afterpotential D (INAD) signaling complex and plastic changes in rhodopsin expression. Furthermore, I discuss the finding that light-dependent shuttling of a signaling protein depends on a second type of cascade that is coupled to rhodopsin.

Anatomy of compound eye

The *Drosophila* compound eye comprises approximately 750–800 reiterating hexagon-shaped ommatidia (Figure 1a), each of which contains 20 cells, including eight photoreceptors. Six photoreceptor cells (R1–6) extend the full depth of the retina, whereas the R7 and R8 cells are situated in the top (distal) and bottom (proximal) halves of the retina, respectively. Thus, only seven of the photoreceptor cells lie in any plane of section (Figure 1b). Photoreception and signal transduction take place in the rhabdomeres, which comprise stacks of microvilli. Approximately 50 000 are present in the larger R1–6 cells (Figure 1c,d). These approximately 1.2–1.5 μm-long microvilli are only approximately 50 nm in diameter and contain an F-actin filament, but are devoid of internal organelles. The secondary retinal pigment cells (RPCs) are the main cells surrounding the photoreceptor cells (2° PC; Figure 1b). Tertiary RPCs and mechanosensory bristle cells occupy alternating vertices of the ommatidia (3° PC and bristle cell; Figure 1b).

In addition to the compound eye, adult flies have three smaller and simpler eyes (ocelli) located on the top of the head. Ocelli seem to be more important for detecting changes in light intensities during flight than for image formation [16].

Fly phototransduction and its relationship to the cascades in rods and cones

Phototransduction cascades serve to amplify single photon responses, and to allow cells to adapt to light with intensities that differ over many orders of magnitude. The initiation of these signaling pathways depend on light sensors that comprise a seven transmembrane-containing protein (opsin) linked to a chromophore (3-hydroxy 11-*cis*-retinal in *Drosophila*, and 11-*cis*-retinal in rods and cones). Light promotes isomerization of the chromophore to the all-*trans* configuration, thereby inducing a conformation change in the protein subunit. The photoactivated visual pigment stimulates GDP–GTP exchange in a heterotrimeric G-protein. In the fly eye, the G-protein (Gq) [17] activates the PLC encoded by *norpA* [18], which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2), leading to opening of the TRP channel and the related TRP-like (TRPL) cation channel in photoreceptor cells (Figure 2) [19–23]. NORPA also accelerates the intrinsic GTPase activity of the Gqα [24–26]. Thus, NORPA promotes activation and negative feedback regulation through distinct domains [24–26]. The increase in Ca^{2+} is counterbalanced by extrusion through the Na^{+}–Ca^{2+} exchanger, CalX [27].

Several of the key aspects of *Drosophila* phototransduction are distinct from the cascades in mammalian rods and cones. In flies, rhodopsin is bistable (i.e. the chromophore usually stays bound to the opsin following exposure to light) [28]. A second photon of light is necessary to convert the 3-OH-all-*trans* retinal back to the 3-OH-11-*cis*-retinal. If the flies are exposed to blue (480 nm) light, the major rhodopsin (Rh1) remains active in the dark. In rods and cones, the light-activated chromophore, all-*trans*-retinal, is released from the opsin and must be recycled through an enzymatic pathway [29,30]. The heterotrimeric G-protein that is activated by the mammalian visual pigments (transducin; G_t) stimulates a phosphosphodiesterase, causing a decline in cGMP levels and subsequent closure of the cGMP-gated channels [31]. Thus, light induces opposite affects on the state of the

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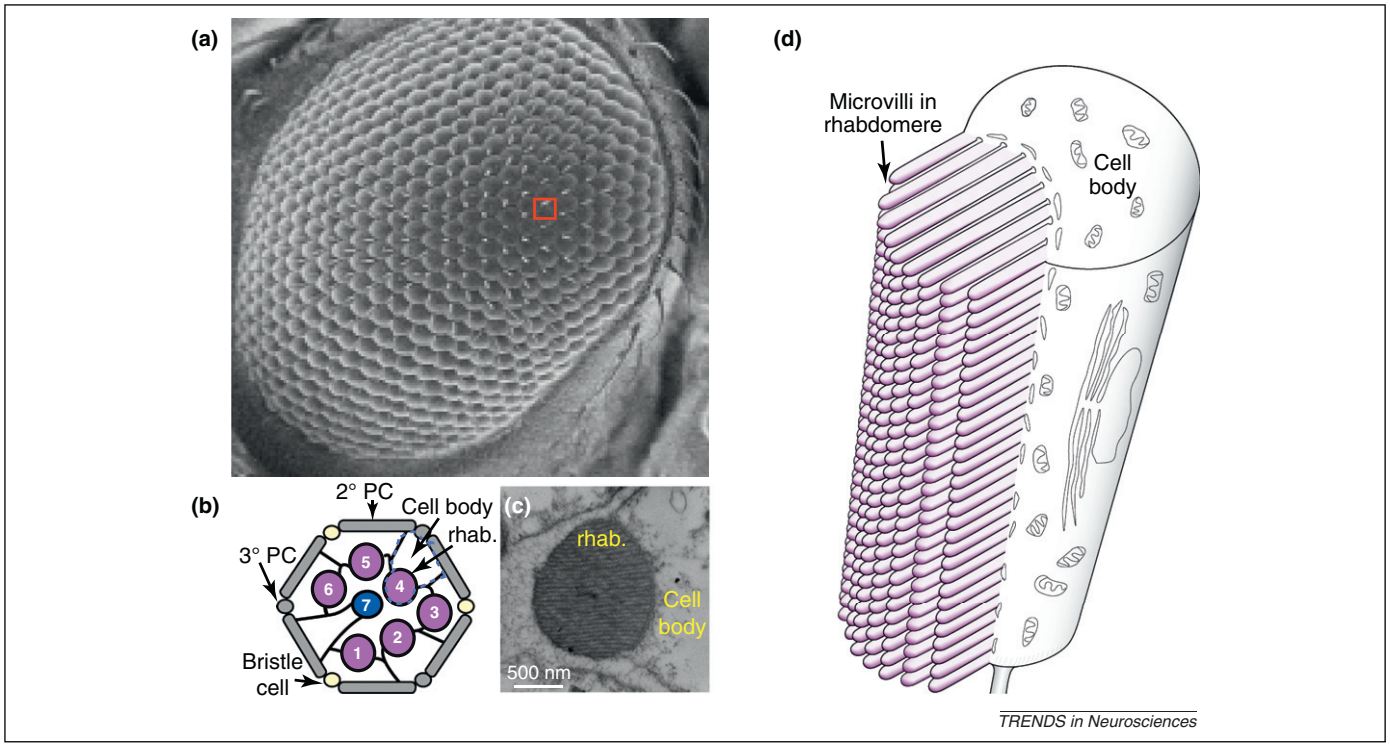

Figure 1. Anatomy of the *Drosophila* compound eye and photoreceptor cells. **(a)** Scanning electron microscope (SEM) image of an adult compound eye. The eye contains approximately 750–800 ommatidia. The red box indicates one ommatidium. **(b)** Cartoon illustrating the various cell types in a cross-sectional view of an ommatidium (distal region). Seven photoreceptor cells, each containing a rhabdomere, are shown: bristle cell, mechanosensory bristle cell; cell body, photoreceptor cell body; rhab., rhabdomere; 2° PC, secondary retinal pigment cells; and 3° PC, tertiary retinal pigment cells. The broken blue line indicates a single photoreceptor cell. **(c)** Transmission EM cross-section through one photoreceptor cell. **(d)** Cartoon showing a longitudinal view of one photoreceptor cell. Approximately 50 000 microvilli are present in the rhabdomeres of each R1–6 cell. The microvilli are not drawn to scale. Normally, there are 30–35 (50-nm wide) microvilli per cross-section.

cation channels in the rhabdomeres, and in the outer segments of rods and cones.

Mammals sensing light like flies

Direct light activation of the ipRGCs is mediated by the visual pigment melanopsin, which bears greater sequence homology to fly rhodopsin than to the mammalian rod and cone visual pigments [5,8,10]. Similar to the major *Drosophila* rhodopsin (Rh1), melanopsin is maximally activated by blue light, and appears to be a bistable photopigment [7,32].

A variety of pharmacological, electrophysiological and expression studies in heterologous systems and in native

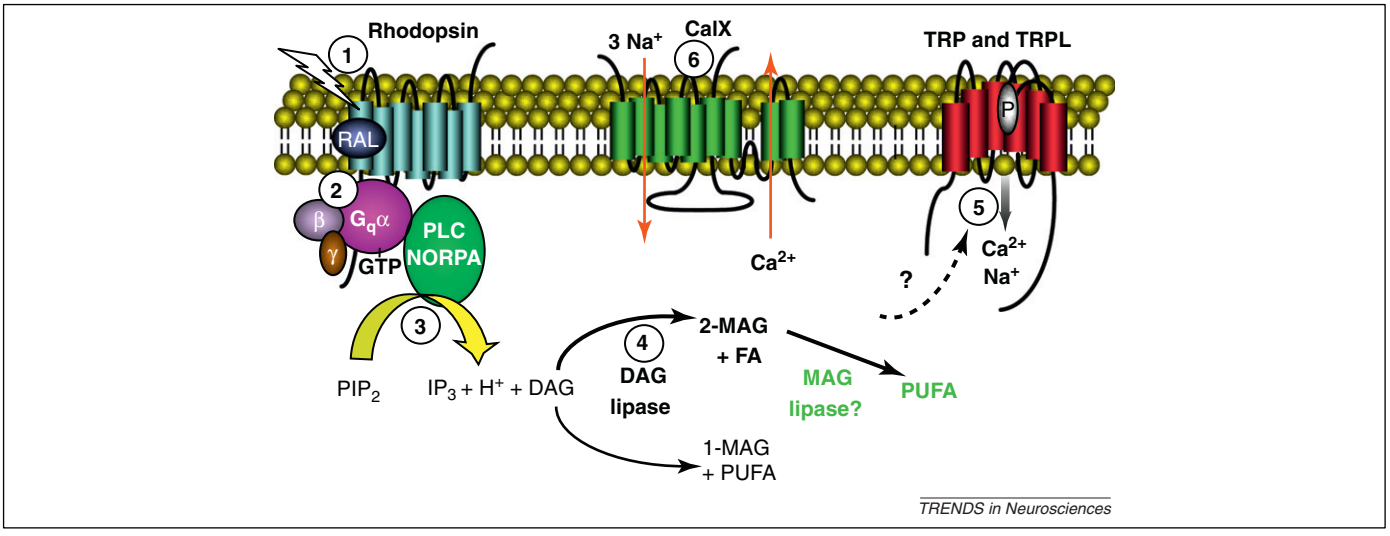

Figure 2. Model of the *Drosophila* phototransduction cascade. Events in phototransduction: (1) light activates rhodopsin; (2) coupling of light-activated rhodopsin with the heterotrimer Gq protein. The activated Gqα subunit associates with GTP; (3) stimulation of PLC leads to hydrolysis of PIP_2 and production of IP_3, DAG and H^+; (4) a DAG lipase encoded by *inaE* hydrolyzes DAG to produce 2-MAG and FA. Minor products are 1-MAF and PUFA. The 2-MAG might be metabolized into PUFA by an unknown MAG lipase; (5) TRP and TRPL are activated following PLC stimulation, although the mechanism remains controversial; and (6) following activation of the channels, a Na^+–Ca^{2+} exchanger (CalX) extrudes Ca^{2+} out of the photoreceptor cell. Abbreviations: DAG, diacylglycerol; FA, saturated fatty acid; IP_3, inositol 1,4,5-trisphosphate; MAG, monoacylglycerol; PIP_2, phosphatidylinositol 4,5-bisphosphate; P, pore loop indicated in TRP; PLC, phospholipase C; PUFA, polyunsaturated fatty acid; RAL, the chromophore (3-OH-11-*cis*-retinal); TRP, transient receptor potential (channel); TRPL, TRP-like.