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Photoreceptors: Unconventional Ways of Seeing

Animals perceive light typically by photoreceptor neurons assembled in eyes, but some also use non-eye photosensory neurons. Multidendritic neurons in the body wall of *Drosophila* larvae have now been shown to use an unconventional phototransduction mechanism to sense light.

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For animals, visual information is vital for detecting potential mates, food, predators or prey. Light is primarily sensed by image-forming photoreceptors in eyes or eye-like structures. Photoreceptor neurons detect photons and generate electrical responses, through a process called 'phototransduction'. However, eyes are not the only organs perceiving light. Unconventional types of non-image-forming light perception are crucial for regulating physiological functions such as circadian rhythms, pupillary reflex or acute suppression of locomotor behaviour in rodents [1–3]. Such non-image-forming photoreceptors have been known to exist since the 1930s in invertebrate species such as the marine gastropods *Aplysia* and *Onchidium* [4]. More recently, similar photoreceptors, the so-called 'intrinsically photosensitive retinal ganglion cells' (ipRGCs) have also been described in mammals [5,6]. Perhaps more surprising was the discovery of non-image-forming photoreceptors in the eyeless nematode *Caenorhabditis elegans*, which has no morphologically distinguishable photoreceptors and lacks genes encoding opsins — the light-sensitive G-protein coupled receptors (GPCRs) used in canonical phototransduction pathways of animal photoreceptors [7]. Now, in a recent paper, Xiang and colleagues [8] show that the *Drosophila melanogaster* larval body wall possesses non-image-forming photoreceptors. In *C. elegans* as well as in *Drosophila,* non-image-forming photoreceptors seem to play a central role in light-avoidance behaviour. Even more surprising is the finding that neither of these non-image-forming phototransduction pathways involves an opsin-related light-sensing protein.

Animal photoreceptor cells come in two principal types characterised by distinct specialized structures that harbour the light-sensing proteins. In ciliary photoreceptors, the light-sensing proteins are housed in a folded ciliary membrane, while in the rhabdomeric type they sit in a folded apical cell membrane forming a rhabdom. While both photoreceptor types may coexist in the same organism, ciliary photoreceptors are typically found in vertebrates and rhabdomeric ones in invertebrates (Figure 1A,B) [9]. The canonical phototransduction pathway in the ciliary photoreceptors of vertebrates involves the ciliary-opsin (c-Rh). Light brings c-Rh to an excited state, in which it activates the G-protein alpha subunit ($G_{t\alpha}$), thereby stimulating a phosphodiesterase (PDE) that hydrolyzes cyclic GMP (cGMP) to GMP. Consequently, free cGMP decreases, causing the closing of the cyclic-nucleotide-gated (CNG) ion channels that are open in darkness. As a final response, the cell hyperpolarizes, thus reducing or arresting the release of the neurotransmitter glutamate [9]. In invertebrates, another canonical pathway operates, established mainly based on the *Drosophila* photoreceptor as a model. It involves the rhabdomeric photoprotein r-opsin (r-Rh). Absorption

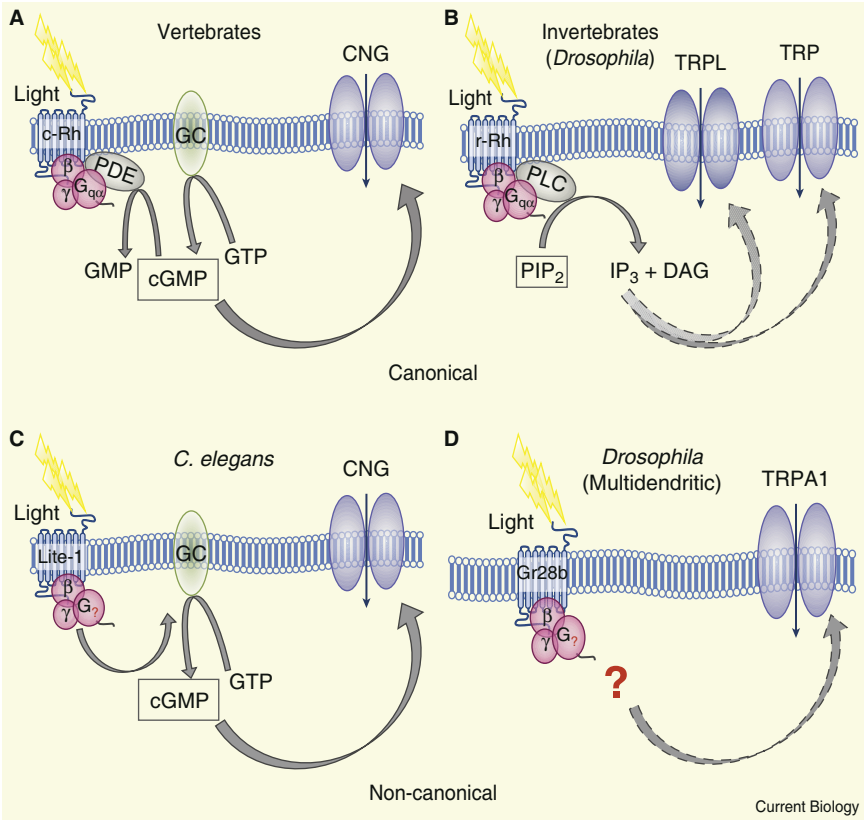

Figure 1. Canonical and non-canonical phototransduction pathways.

(A,B) Representation of canonical phototransduction pathways, as described for vertebrate rod photoreceptors (A) and invertebrates (*Drosophila*) (B). (A) In canonical phototransduction pathways in vertebrates light activates the photosensitive ciliary opsin protein (c-Rh), which activates the formation of the G-protein–phosphodiesterase (PDE) complex. Active PDE hydrolyzes cyclic GMP (cGMP), thereby activating the cyclic-nucleotide-gated (CNG) channels. (B) Canonical phototransduction in invertebrates proceeds in the same manner with the G-protein cascade, but it uses a rhabdomeric (r-Rh) opsin, phospholipase C (PLC) that hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG). IP_3 and DAG activate the transient receptor (TRP) channels. (C,D) Novel non-canonical phototransduction pathways, one found in *C. elegans* (C) and another in *Drosophila* larvae multi-dendritic neurons (D). G-protein cascades also mediate both non-canonical pathways. (C) In *C. elegans*, the gustatory receptor Lite-1 is the photosensitive protein that activates the G-protein, which stimulates guanylate cyclases (GC) to convert guanosine tri-phosphate (GTP) in cGMP, activating the CNG channels. (D) Non-canonical phototransduction pathway in *Drosophila* uses the gustatory receptor Gr28b that activates the G-protein and subsequent activation of the transient receptor TRPA1 channel via a mechanism that is not yet known. Red question marks indicate lack of evidence for the respective components. Dashed arrows indicate that the exact mechanism of channel activation remains elusive.

of a photon activates r-Rh, which then activates the alpha subunit of G-protein ($G_{q\alpha}$) that binds to and activates phospholipase C (PLC). This in turn hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG). As a result, two classes of light-sensitive transient receptor channels (TRP and TRPL) are open, thus depolarizing the cell.

Recently, two surprising discoveries [7,8] revealed novel non-canonical phototransduction pathways in which light-sensing is mediated via GPCRs of the gustatory receptor family (Figure 1C,D). The first non-canonical pathway was described in *C. elegans* [7]. Instead of a classical *opsin*, phototransduction makes use of *lite*-1, a gustatory receptor type GPCR. Phototransduction in *C. elegans* requires guanylate cyclases but not PDEs as in the vertebrate canonical pathway. Thus, Liu and colleagues [7] proposed an unusual mechanism for the regulation of cGMP-sensitive CNG channels, according to which guanylate cyclase is modulated via G-protein signaling. A similar mechanism might exist in some marine invertebrates to regulate K^+ channels [10]. Now, in a recent study by Xiang and colleagues [8], a different non-canonical pathway has been identified in *Drosophila* larvae [8]. Intriguingly, photoreceptors are covering the complete body of the larvae in a network-like fashion, allowing an alternative mode of light perception. Using genetic analyses, Xiang and colleagues [8] showed that class IV multidendritic neurons are activated when the larval body wall was exposed to light. As the name suggests, multidendritic neurons typically possess a single axon and multiple dendrites that terminate freely under the epidermis [11]. These neurons are responsible for thermo- and mechanosensation [12–14], but further experiments ruled out that temperature, concentration of reactive oxygen species or touch could be the cause of neuronal firing the authors observed in response to illumination. Thus, Xiang and colleagues [8] concluded that multidendritic neurons of class IV in *Drosophila* are also photosensory neurons. Primary neuronal cultures of these neurons showed activation by ultraviolet, violet, and blue light but not green or red light. Genetic analysis strongly suggests that gustatory receptor *Gr28b,* the closest *Drosophila* relative of *lite*-1 is the photoreceptor, but direct evidence is as yet lacking. In the *Drosophila* non-canonical pathway, G-protein signalling is also required. In contrast to *C. elegans*, transduction does not seem to act through CNG channels; instead, *TrpA1*, a member of the TRP ion-channel family, is the channel responsible for phototransduction.

Drosophila larvae have simple eyes known as ‘Bolwig organs’ that use the canonical invertebrate phototransduction pathway and the same rhodopsins (rh5 and rh6) as adult R8-photoreceptors [15,16]. Xiang and colleagues [8] also performed behavioural analysis on *Drosophila* larvae lacking Bolwig organs and wild-type larvae by exposing them to different light intensities. Larvae both with and without eyes avoided high light intensity. At lower intensities, wild-type larvae were more effective in avoiding light than eyeless larvae. This suggests that the larval eyes are preferentially used for avoidance of dim light whereas class IV multidendritic neurons act in light avoidance under

high light intensity such as sunlight. Thus, these two parallel photosensory pathways seem to complement each other.

Photoreceptors of the Bolwig organ are involved in essential light responses such as light-avoidance and circadian rhythm control and are presumed to respond exclusively to light using rhodopsins [17]. Conversely, the majority of reported non-image-forming photoreceptive neurons can also sense thermal, mechanical and chemical stimuli [4,8]. This has led to the idea that different types of information (light, thermal and mechanical) should be integrated by a single type of neuron to elicit a behavioural response. Xiang and colleagues [8] propose that a possible behavioural function for class IV multidendritic neurons is nocifension — a behavioural response to potentially harmful stimuli. Class IV multidendritic neurons are required for thermal and mechanical nociception [18]. Avoidance of strong light mediated by multidendritic neurons may also be a nocifensive response to the risk of desiccation in sunlight. Interestingly, *Drosophila* larvae are able to perform rather complex tasks, for instance to learn and memorize when light is associated with other sensory stimuli [19]. However, evidence on whether the unconventional light sensors mediate such learning remains elusive.

The discovery of non-canonical phototransduction pathways using unexpected sensory neurons raises exciting questions about the molecular nature of these pathways and how distinct photosensory neuronal networks act to integrate sensory information.

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