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The Multifaceted Roles of Opsins in Sensory Reception

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ABSTRACT

Opsins are known for their transmembrane signalling, through activation by light, enabling image-forming vision. However, they are represented not just in the retina but the brain and extra-cephalically throughout animal tissues, including the skin. What are they doing? Investigation of sensory modalities and genetics in the fly, *Drosophila,* has helped make the evolution of these proteins and their functional development clearer and shown a remarkable commonality to the role of opsins in mammalian sensory development, structure and function, helping to reveal the importance of their contribution to the evolution of mammalian anatomy and physiology.

Introduction

As a skin cancer physician, I was surprised to find opsins, expressed in the skin. Opsins, traditionally understood as photoreceptive proteins, play a significant role in the visual processes by detecting light and contributing to the formation of images. My initial reaction was to consider these proteins to have a light-responsive function. This has turned out to be a one-dimensional view. Further reading has shown that these proteins have non-image forming functions, even within the retina, such as circadian photoentrainment. However, recent studies have broadened our understanding, revealing that opsins are not exclusively light sensors. Light-independent roles for opsins in multiple sensory modalities are emerging.

In Drosophila, opsins have been shown to be involved in thermal behaviour, hearing, proprioception and taste. These proteins are part of a complex network that allows organisms to perceive and adapt to their environments through multiple sensory inputs.

Opsins in mammals are now recognized as polymodal sensory receptors, this finding is significant as it opens new avenues for exploring how sensory information is processed and integrated within the nervous system.

The discovery of these non-traditional roles of opsins is reshaping our understanding of sensory reception. It challenges the conventional view that opsins are solely light sensors and highlights their critical involvement in a broader range of physiological processes. As research continues, it is likely that even more functions of opsins will be uncovered, providing deeper insights into the intricate mechanisms of sensory perception.

Evolution of opsins

All known visual pigments in neuralia (cnidaria, ctenophora and bilateria) are composed of an opsin (7 transmembrane G protein-coupled receptor) and a light sensitive chromophore, generally retinal[1]. Consequently, opsins play a key role in vision. Despite some controversy in phylogenic relationships within the neuralian opsin subfamilies, it is agreed that opsins and melatonin receptors share a common ancestor. Further, all neuralian opsins can be classified into 3 subfamilies, ciliary, rhabdomeric and G_o/retinal G protein-coupled receptor opsins. According to Feuda et al, confirming the results of Fredrikson et al[2], the first opsins originated from the duplication of the common ancestor of the melatonin and opsin genes in a eumetazoan ancestor, and an inference of its amino acid sequence suggests that this protein might not have been light sensitive. It is theorised that two more gene duplications in the neuralian lineage resulted in the opsin subfamily members and therefore the first animal to express these proteins was a neuralian, rather than bilaterian, progenitor[3]. These results differed markedly from previous results and hypotheses [4,5]. They further suggested that the gene duplication took place during a short 11-million-year period, approximately 700 mya and that this was earlier than currently accepted and the progenitor was probably also more complex than previously thought[6].

New light on Photoreceptive cell evolution

Views on animal photoreception are dominated by analysis of pigmented cephalic eyes[7], which are prominent in most branches of animal evolution. However, eyes and other photoreceptive cells (PRCs) are present outside of the brain, with multiple examples among bilaterians. Drosophilae possess PRCs in the larval body wall mediating a photo avoidance response[8]. Sea urchins possess PRCs in their tube feet[9] and the basal chordate, amphioxus, displays a series of phototypical visual organs (a PRC with associated pigment cell) located along the ventral neural tube referred to as ocelli[10]. These segmental organs could reflect ancient sites of photoreception that predate the cephalisation of body plans and may still retain functions that complement cephalic PRCs[11]. Even in zebrafish (a vertebrate model) two orthologs of *Platynereis* opsin are expressed in mechanoreceptive cells, neuromasts of the lateral line, a link between mechanic and photic senses.

Opsins functioning as thermo-activated receptor proteins

Shen et al identified that the ability of *Drosophila* larvae to choose their ideal temperature (18°C) depends on a thermo-sensory signalling pathway that includes a G_q protein, a phospholipid C (PLC) and a transient receptor potential TRPA1 channel[12]. It had already been recognised that a thermo-sensory signalling cascade was required in the nematode worm, *Caenorhabditis elegans*, but this included guanylate cyclase and a guanosine 3',5'-monophosphate (cGMP) -gated channel. They went on to show that mutation of a gene, (*ninaE*), that encodes *Drosophila* rhodopsin eliminated this thermotactic discrimination. It was also shown that this thermotactic role for rhodopsin was light-independent because thermotaxis takes place in the dark[13], although they found that binding to a chromophore was still required.

A unique characteristic of mammalian sperm thermotaxis is extreme temperature sensitivity with the capacity to respond to temperature changes of <0.0006°C as they swim their body length distance. Pérez-Cerezales et al showed that the sensing system involves opsins which are known to be G protein coupled receptors (GPCRs). They showed that sperm thermotaxis involves two signalling pathways, the PLC and the cyclic-nucleotide pathway Figure 1. Mammalian opsins acting as not only photosensors but also thermosensors[14].

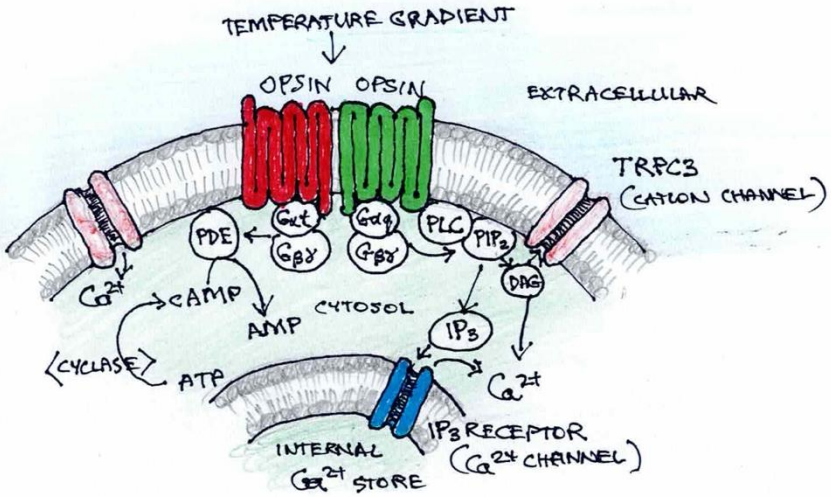

Figure 1. Involvement of two signalling pathways in sperm thermotaxis.
The PLC pathway is shown on the right and the cyclic nucleotide pathway on the left.

Hearing and auditory organ genes in Drosophila

The *Drosophila* hearing organ shares similar transduction mechanisms with vertebral hair cells, and both are specified by *atonal* family genes.

Senthilan et al showed that auditory stimulus processing involves chemoreceptor proteins and photoreceptor components. Their findings demonstrated that mechanosensory roles for ionotropic receptors and visual rhodopsin, indicating that different sensory modalities utilise common signalling cascades[15].

One of the genetic model organisms used to study auditory relevant genes is *Drosophila*, which communicates via courtship songs and hears with antennal ears[16]. The *Drosophila* ear is composed of a sound receiver and an auditory sense organ. The sound receiver is formed by the 3rd antennal segment and its arista[17]. Vibrations are transduced by Johnson's organ, an array of ~250 chordotonal sensilla in the 2nd segment Figure 2. These also serve wind and gravity sense[18]. Sensilla are composed of mechanosensory neurons, their lineage specified by the transcription factor atonal (Ato)[19], whose homolog AtoH1 directs the formation of hair cells in vertebrate ears[20]. These sensilla and hair cells share other proteins and transient receptor potential (TRP) channels, both cell types employ equivalent transduction modules to achieve amplification of mechanical input.

Ato specifies *Drosophila* chordotonal organs, photoreceptors and chemosensory coeloconic sensilla[21,22]. All these receptors are thought to have evolved from an *ato*-dependent protosensory organ that is presumed to consist of chordotonal sensilla serially arranged along the body and distributed widely among arthropod groups[23]. Photoreceptors detect light with rhodopsin and chemoreceptors detect volatile chemicals with ionotropic glutamate receptors, which mediate neuronal communication at synapses throughout vertebrate and invertebrate nervous systems[24].

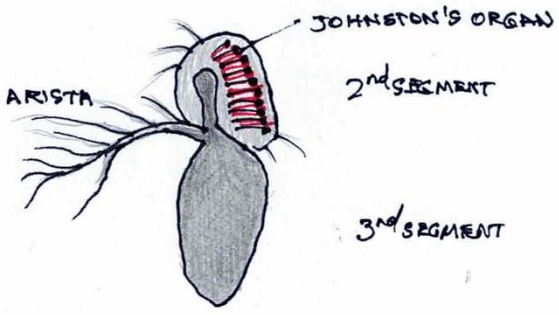

Figure 2. A representation of the *Drosophila* antenna and arista.
The 2nd and 3rd segments are depicted with Johnson's organ (red) consisting of chordotonal sensilla.

Rhodopsins are expressed in Johnston's organs and their disruption seriously impairs neuron function required for mechano-transduction channel gating. Apart from detecting photons and light they serve other sensory functions[25].

The involvement of rhodopsin and ionotropic receptors in mechanosensory chordotonal organs suggests these proteins served roles in sensation before chemo-and photoreception diversification, helping gain a clearer understanding of the evolution of sensory modalities and signalling cascades.

Opsins in *Drosophila* taste

Animals rely on contact chemosensation to evaluate food quality. The chemical perception of food is initiated through the binding of tastants to receptor proteins expressed in peripheral gustatory receptor cells, the information transmitted to the central nervous system that then determines to ingest or reject food.

It was initially thought that taste in insects was through ligand-gated cation channels. A limitation of ionotropic receptors is that they do not allow for amplification which would enable the fly to detect tastants in small concentrations.

Kim et all showed that detection of the plant-derived bitter compound aristolochic acid (ARI), in the *Drosophila*, depends on a G protein, G_q, phospholipase C (PLC)-β, and transient receptor potential (TRP) Al amplification cascade (6). This is similar to mammalian taste receptors that couple to a PLC signalling cascade with activation of TRP channels[26].

Leung et al found three Drosophila opsins, Rh1,4 and 7, were needed for ARI sensation at low concentrations. Flies respond to higher concentrations of ARI through direct activation of TRPA1 channels.

These findings provide the first demonstration that opsins function in chemo-sensation. The gustatory requirements for these opsins are light-independent, not requiring retinal chromophore binding. They proposed that rhodopsin represents a class of polymodal sensory receptors with roles as potentially diverse as TPR channels[27].

Unconventional roles for opsins

The observation that opsins are not just photodetectors but have light-independent roles in thermosensation, hearing and taste raises the question of their primordial function. Responses to temperature, touch and taste are primitive senses that predate light sensation and only require one component, the opsin. Opsins that function in *Drosophila* temperature and hearing require the chromophore, likely co-opted to serve as a molecular chaperone. Again, reinforcing the view that light-independent roles for opsins may have arisen prior to light sensation.

Two central functions of rhodopsin-dependent signalling are signal amplification and adaptation[28]. These roles are employed in other sensory contexts. The amplification cascade allows low levels of stimulus to be detected. If the stimulus cannot be avoided but is present at low concentrations, that is not dangerous, then the organism adapts.

The repertoire of senses that depend on opsins is likely to be greater than currently recognised. What is clear is that they represent a broad class of polymodal sensory receptor.

A conserved developmental program for sensory organ formation

It was initially thought that different sensory organs such as the eye and the ear had separate origins driven by distinct organ specific factors. Niwa et al, however, suggest that diverse sensory organs might arise by segmental-specific modifications of a general developmental program for sensory organ formation[23].

They found that in *Drosophila,* a common proneural gene, atonal (*ato*) functions in the initial process of development of segment-specific organs, the compound eye, Johnston's auditory organ and a stretch receptor, the chordotonal organ in the leg[22,29], suggesting a common evolutionary origin.

They showed that integration of decapentaplegic (*dpp*), wingless (*wg*) and ecdysone signals into a single *cis*-regulatory element of *ato*. Induction of ectopic eyes by *ey* does not induce the entire eye morphogenic program but modifies *ato*-dependent neuronal development.

They suggest that various sensory organs evolved from an *ato*-dependent protosensory organ through segment specification by *ey* and *Hox* genes. They found that Johnston's organ and the chordotonal organs formed simultaneously with eye formation, positioning controlled by morphogenesis dependent *dpp* and *wg*. Induction, requiring the hormonal factor ecdysone, allowing expression of ato, the common entry site for spatiotemporal signals.

As the development of vertebrate sensory organs has many molecular similarities to that of sensory organs in *Drosophila*, similar mechanisms of sensory organ diversification might also have functioned in the evolution of the vertebrate body structure[23].

Locomotion and proprioception

Locomotion is one of the defining features of animal life and the need for movement control would have been a driving factor in early nervous system evolution[30,31]. A key component of movement control is proprioception, providing mechanosensory feedback to inform the CNS about locomotory body movement. Zanini et al identified that, in *Drosophila,* movement control required visual opsins. Opsins were identified in chordotonal proprioceptors along the larval body, localised to their cilial dendrites and the receptors were found to express the opsin genes *ninaE, Rh6* and *Rh7*. Disrupting *Drosophila* opsins NINAE or RH6 impaired larval locomotion and body contractions, independent of light and vision. As well as implicating opsins in movement control, non-ciliary, rhabdomeric opsins played a role in cilium organisation. Loss of opsins not only impaired mechanically evoked proprioceptive spiking but also cilium ultrastructure. This

suggests that structural roles for opsins may have preceded their sensory role[32].

Opsins are implicated in sensory dendritic maintenance

Mechanotransduction in *Drosophila* lch5 receptors takes place in the cilia, but NINAE and Rh6 localise beneath the cilia to the dendritic inner segment which harbor the ciliary rootlets, which support cilia structurally and are essential for cilial maintenance[33]. Figure 3.

The dendritic localisation of NINAE beneath chordotonal receptors might reflect evolutionary transition, suggesting that the structural roles of r-opsins in sensory dendrites proceeded their use for light detection. They possibly helped shape dendritic membrane composition given that opsin have been found to act as membrane transporters, translocating phospholipids between the two membrane leaflets[34]. From work on photon and chordotonal receptors in *Drosophila,* it appears that structural r-opsin function might have been preserved during sensory receptor cell evolution, explaining why diverse sensory modalities depend on opsins[32].

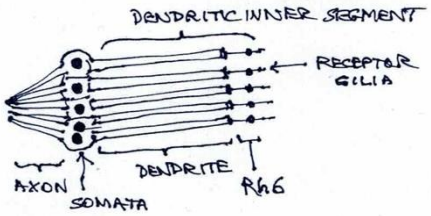

Figure 3. Opsin expression and localisation in *Drosophila* proprioceptors
Diagrammatic representation of the five receptor cells of lch5, the *Drosophila* lateral chordotonal organ serially arranged along the larval abdomen.

Opsin is a phospholipid flippase

Polar lipids must cross biological membranes to sustain life. A phospholipid molecule in a membrane bilayer can diffuse through one leaflet but faces a barrier to the translocation of its polar head-group through the hydrophobic interior of the membrane to the other leaflet. Photoreceptor discs possess an assortment of membrane proteins that act as lipid transporters that translocate phospholipids across cell membranes, flippases, coupling ATP hydrolysis to provide unidirectional lipid flipping. Menon et al demonstrated that opsins act as ATP-independent bidirectional flippase in photoreceptor disc membranes[34]. The value of opsins to visual systems is not only their combination with a chromophore enabling light-induced conformational changes but also their assistance in rapid, low-cost transmembrane movement of the chromophore for re-isomerisation. Investigations raise the possibility that the ability to flip lipids may extend to many members of structurally related GPCRs as integral membrane signalling proteins.

Opsin structure in other conformational changes

Opsins are heptahelical proteins like other GPCRs. Their seventh transmembrane domain (TM7) contains a conserved lysine-residue that binds the retinal chromophore via a Schiff-base-linkage[1] enabling light-induced conformational changes, however, other conformational changes are possible e.g. phospholipid scrambling by bovine opsin can form a hydrophobic cavity/groove[35,36] allowing the protein to act like a 'credit-card-reader' enabling phospholipids to swipe their way between membrane leaflets with the head group dragging the hydrophobic tail through the membrane core[37]. Groove dilation deforms the membrane bringing the two bilayer leaflets together facilitating phospholipid flipping at the protein membrane interface[38]. These changes are independent of photoisomerization of retinal[36]. Certain tastants can fit the chromophore binding pocket of opsins[27] suggesting a range of structure-function activation possibilities. Perhaps, instead of asking what came first, light or non-light function it is more reasonable to say the opsins have evolutionary light-dependent and light-independent functional possibilities.

Conclusion

It appears that opsins developed through evolution as polymodal sensory receptor proteins with important amplification and adaptive functions as part of an adaptive developmental toolkit with multiple applications. This extends the functional role of opsins beyond image-forming vision to diverse sensory modalities but still does not satisfactorily explain their ubiquitous distribution throughout most mammalian tissues. Their role in the transmembrane transport of lipids in a context of structure as well as function may provide the answer. Opsins have the ability to provide ATP-independent, very rapid lipid transfer across biological membranes. The importance of lipid scrambling is significant not only in diurnal phagocytosis of photoreceptor outer segments in the disc membrane but also in various physiological contexts, ranging from blood clotting and the clearance of apoptotic cells to the growth of cell membranes and protein glycosylation in the endoplasmic reticulum.

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