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Lost in phototransduction: a few facts and hypotheses on cephalopod photoresponse

Francesco Moccia[1], Carlo Di Cristo[2], Anna Di Cosmo[1]

[1]Department of Structural and Functional Biology, University of Naples, Federico II, 80126 Naples, Italy, [2]Department of Biological and Environmental Sciences, University of Sannio, 82100 Benevento, Italy

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1. ABSTRACT

Cephalopods are endowed with the most sophisticated nervous system among invertebrates and exhibit a repertoire of complex behaviors, such as spatial and observational learning. Cephalopod eyes supply a wide range of information which are utilized for these learning behaviors. Although our understanding of vertebrate physiology greatly benefited from the sub-cellular analysis of cephalopod nervous system, as shown by the discovery of the ionic bases of action potentials and of the Ca2+ requirement for neurotransmitter release Surprisingly, the cellular basis by which the visual system drives the sophisticated repertoire of cephalopod behaviors are still poorly understood. In this review, we will describe the current knowledge about cephalopod phototransduction. Light excites cephalopod photoreceptors by either inducing Ca2+ release from intracellular stores or activating cation-permeable channels by an as yet unknown mechanism. A 92 kDa protein, which is homologous to the Drosophila transient receptor potential (TRP) gene, is the most likely mediator of light-induced currents in cephalopods. A number of models which explain the mechanism whereby cephalopod TRP channel is gated by light will be discussed.

2. INTRODUCTION

Cephalopods are an ancient group of molluscs, which currently encompasses two major divisions: the nautiloids, virtually extinct represented by the single genus *Nautilus*, and the modern coleoids, containing all other living cephalopods, such as octopus, cuttlefish and squid (1). Coleoid cephalopods are endowed with the largest and most complex nervous system among the invertebrates (2), which rivals that of many vertebrates, including reptiles and fish, and retains the ability to integrate a variety of peripheral sensory inputs in order to produce the most appropriate behavioral output (3, 4). In this view, many of the sensory organs which guide cephalopod life (e.g. camera eye and statocyst) share significant parallels with their analogous structures in vertebrates (4, 5), while the "effector" systems may be unique to coleoids (e.g. chromatophore organs). In addition, it has recently been shown that the chambered nautilus (*Nautilus pompilius*), although lacking the dedicated neural regions that support learning and memory in all other extant cephalopods, may express a mnemonic behaviour similar to that displayed by coleoids (7). The wealth of information on the behavioral repertoire of cephalopods (among which observational learning is the most fascinating one) is not accompanied by

an analogous understanding of the sub-cellular mechanisms governing stimulus detection, signal integration in the central nervous system (CNS) level and response activation (2, 6). The exception is provided by the squid giant axon, the fiber that innervates mantle muscles and controls the jet-propelled escape response of the animal, perhaps being the most intensively studied system in neuroscience (8). Accordingly, the large size and easy handling of this structure first led to the elucidation of ionic basis of action potentials by Hodgkin and Huxley (9). Subsequent work on the chemical nature of the giant axon synapse resulted in the formulation of the Ca^{2+} hypothesis of neurotransmitter (i.e. glutamate) release (reviewed in 10). Notably, the latter discovery opened a new avenue of research aimed at exploring the large number of cellular processes regulated by changes in cytosolic Ca^{2+} levels (11, 12). Therefore, it appears that unraveling the intracellular pathways triggered by plasmalemmal receptors, which either sense environmental stimuli or bind to neurotransmitters released by afferent fibers, in cephalopods might advance current knowledge of signal transduction mechanisms in vertebrates. In agreement with this hypothesis, brain slice electrophysiology on octopus vertical lobe, the area involved in complex forms of learning, showed that similar cellular processes may mediate sophisticated behaviors in phylogenetically remote animals (13). This review will focus on the signalling pathways activated by light in cephalopod photoreceptors, which have long provided an ideal model to investigate cell surface receptors-induced production of intracellular second messengers, such as inositol-1,4,5-trisphosphate ($InsP_3$) (5). In addition to highlighting the possible implications for vertebrate cell physiology, which might emerge from study of the phototransduction cascade in cephalopods, we will focus on the lack of information about the photoresponse downstream of $InsP_3$ synthesis. The most recent insights provided by biochemical and electrophysiological techniques will be discussed in the light of the latest advances in the Ca^{2+} signalling area (11, 12).

3. CEPHALOPODS AS VISUAL ANIMALS

The rationale behind a detailed survey of light-induced intracellular pathways in cephalopods is that the latter are highly 'visual' animals whose survival depends on their ability to detect any novel object, such as prey or a predator in their visual field (14, 15). The complex organization of cephalopod eye (see Paragraph 4), and associated optic and supraoesophageal lobes (16; see below), may be explained by their evolution in competition with other highly developed sea creatures such as fish (6) . For instance, it has been shown that octopuses can discriminate visually between two targets differing in size, brightness, shape, orientation and polarized light (1, 17). In one experiment, an octopus was allowed to attack and eat a crab presented on a square background, but given a mild electrical shock when a crab was presented on a rectangular background. After only a few trials the octopus no longer attacked in the presence of a rectangle, thus showing an ability to discriminate the differences between the two similar shapes (17). In subsequent experiments, octopuses failed at discrimination between a square and a circle, but were able to discriminate between a square on edge and a square on point, or a four centimeter square from an eight centimeter square, even if the larger one was twice the distance away (17). In addition, recent evidence indicates that octopus can use visual landmarks to navigate and find the way back to the den (for a comprehensive review, see 18), which suggests that cephalopods may have a navigational memory. Visual information from the immediate background is also the input driving the changes in pattern, color, brightness/contrast and texture of the skin which result in the production of an astonishing number of body patterns by the animal (19-21). Such a visually-driven behavior allows cephalopods both to camouflage with surrounding environment (22-23) and escape predators (24) and to communicate with cospecifics (21, 25). For instance, recent work performed on the "disruptive" body pattern led to the notion that cuttlefish utilizes a variety of cues, such as well-defined edges, light objects, object area and visual depth contrast (26-27). Interestingly, a similarity has been drawn between cuttlefishes' camouflage behavior and human object recognition (28). It has been shown that the optic lobes, the large central nervous system areas lying just behind each eyes, are instrumental in visual learning and memory storage (29). Consistently, damaging these lobes may dramatically impair the ability to visually learn in behavioral tests (30). For instance, after removing an optic lobe from one side, an octopus will no longer attack when that eye is used to see a crab at a distance (31, 32). The physiology of the eye and the large optic lobes and their association with visual memory lobes makes the animal an apt visual learner. Notably, the vertical lobe of the supraesophageal nervous mass provides a system that prevents octopus attacks following optic lobe lesion (32). This and other ablation experiments suggest that the control of the visual learning system by optic lobes requires the presence of functional vertical lobe (32). However, we may refer reader for a neurophysiological description of these remarkable structures to recent reviews (2, 6). Here, we will only recall that the functional interaction between optic and vertical lobes is likely to provide the neuronal correlate of octopus' ability to learn a task by watching a previously trained demonstrator (33-34), the so-called observational learning (but see 22).

4. THE COMPLEX STRUCTURE OF CEPHALOPOD EYE AS COMPARED TO VERTEBRATES

Cephalopods possess camera eyes, which are among the most highly developed light sense organs in the animal kingdom and show a superficial similarity with those of vertebrates (1, 36), thus providing a text-book example of convergent evolution (36). The eye of the squid, octopus, cuttlefish, and nautiloids is remarkably similar to the vertebrate eye in having a cornea, lens, and retina, but there the resemblance ends (Figure 1A). In these eyes, the pigment (sensory) cells are on top of the retina and receive light directly from the lens (37). In addition, either bipolar and ganglion cells are absent in cephalopod retina, the equivalent structures being located in the outer layers of the optic lobe, sometimes referred to as the "deep-retina" or *retina profunda* (16, 38). A major variation

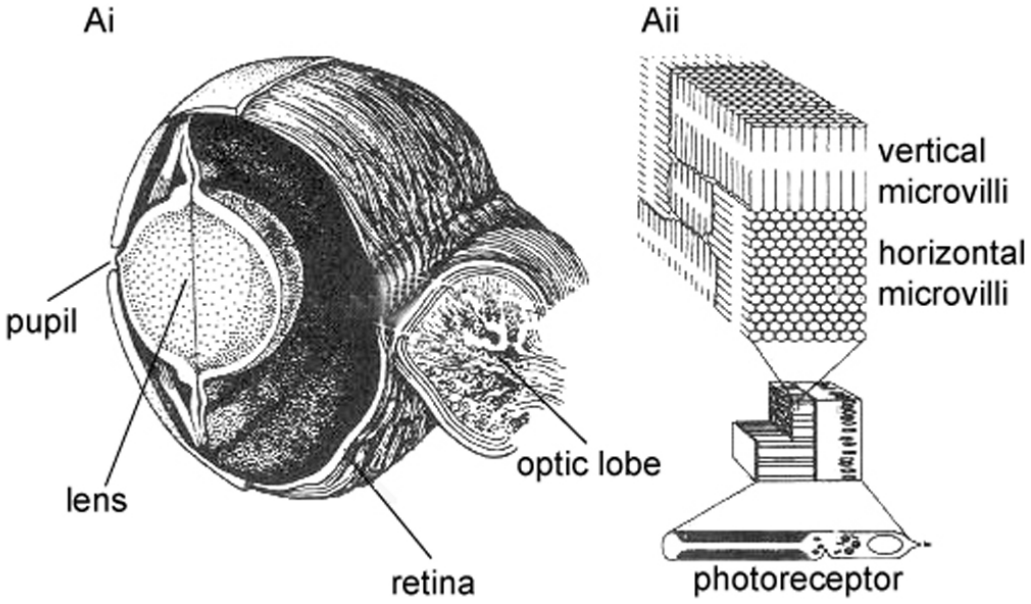

Figure 1. Organization of the visual system in Cephalopods**.** A, the structure of cephalopod eye and the organization of photoreceptor cells (adapted from 1). Ai, schematic drawing showing the pupil, lens and optic nerves leaving the back of the retina and entering the outer region of the optic lobes. Aii, section of retina, with a single retinal cell shown below and the horizontal/vertical arrays of microvilli shown above.

among cephalopods concerns the position of the eyes. Indeed, octopod (such as, *Octopus vulgaris*) eyes are located on the sides of the head with a frontal overlap of about 10°, a feature that endows the animal with a monocular and lateral field of view (29, 39). Conversely, decapod (such as, *Sepia officinalis*) eyes are so situated that their visual field can extend over 360° in the horizontal plane, thus resulting in a binocular vision (15).

Both in Octapods and Decapods, photoreceptor cells are of the rhabdomeric type (2, 40): no rods and cones are present in cephalopod retina. In this view, it is worth mentioning recent evidence that convincingly indicates how both rhabdomeric and ciliary (such as rods and cones) photoreceptors may coexist in Deuterostomia and Protostomia (40). Each cephalopod photoreceptor consists of an outer segment and an inner segment that are divided by a basement membrane. The nucleus of the cell is situated in the latter, while the former points toward the lens and its interior has a central core with an axis that runs down the centre of the cell (37, 41). On the sides of each central axis, there are a series of rectangular projections (rhabdomeres) that are layered on top of each other and are at right angles to the central axes (37). Half the photoreceptors have their rhabdomeres oriented vertically and half oriented horizontally as the eye is held in the orbit (Figure 1B). This orthogonal arrangement provides the basis for detecting the plane of polarized light (42): cephalopods are, indeed, sensitive to the orientation of the *e*-vector of linearly polarized light and, therefore, possess polarization sensitivity (for a comprehensive review, see 43). Rhabdomeres are further organized in rhabdomes, which are formed by four rhabdomeres from four different retinal cells (41). Structurally, rhabdomeres appear as elongated microvilli that increase the surface area available for light absorption and contain the photosensitive pigment, rhodopsin, whose spectral sensitivity peaks at around 480 nm (1). The presence of only one visual pigment is consistent with the observation that cephalopods cannot detect colors and their vision is almost exclusively monochromatic (black and white) (1, 44). Color blindness is a rather puzzling feature, since cephalopods can camouflage themselves against almost any substrate in a chromatically rich environment (25). However, polarization vision might provide information similar to that available from color vision and aid in recognizing objects (45). From the inner segment originates the photoreceptor axon, which exits at the back of the retina (a feature which means that, unlike vertebrate eyes, there is no blind spot), unites with other axons from other photoreceptor cells in the cephalopods choroids, and enters into the sclera (37, 41). These axons gather together to form the optic nerve, which projects to the optic lobes through an inverting optic chiasma (Figure 1A) (41). The retinal photoreceptors mainly terminate in the plexiform zone of optic lobe cortex outer cortex (Figure 1A), where they release both acetylcholine and glutamate (46; see also 47). Notably, the optic lobe may project efferent fibers back to the retina (38), which might establish a synaptic contact with the inner segment of rhabdomeres and modulate screening-pigment migration by releasing dopamine and FMRFamide (48, 49).

An additional difference between vertebrate and cephalopod photoreceptors is that the latter are of the "on" depolarizing sort (50), while the former are hyperpolarized by light absorption (51). Indeed, photoexcited rhodopsin activates cGMP phosphodiesterase (PDE) via

photoreceptor-specific GTP-binding protein, transducin, resulting in the closure of cyclic guanosine monophosphate (cGMP)-sensitive non-specific cation channels and subsequent hyperpolarization of rods and cones (51). The signalling machinery activated by photons in cephalopods utilizes a different second messenger system, such as the PLC/$InsP_3$ pathway, which might explain the different polarity of the photoresponse (5, 52; see next Paragraph). However, it is worth mentioning two recent discoveries that strongly challenge these dogmas. First, the retinas of the scallop and other marine mollusc in endowed with a layer of ciliary photoreceptors that hyperpolarize in response to photostimulation, due to the opening of light-sensitive K^+ channels gated by intracellular cGMP (53, 54). Second, vertebrate retina contains a tiny minority of photosensitive ganglion cells, which mediate a number of physiological responses to daylight, including pupillary responses and synchronization of circadian rhythms (55). This hitherto unknown class of photoreceptor cells is likely to originate from rhabdomeric photoreceptors (56) and employs a membrane-associated phosphoinositide cascade to transduce light signalling (57).

5. THE PHOSPHOLIPASE C (PLC)/INOSITOL 1,4,5-TRISPHOSPHATE ($INSP_3$) PATHWAY IS CENTRAL TO CEPHALOPOD PHOTOTRANSDUCTION

Along with *Limulus* ventral eye and spontaneously occurring *Drosophila* mutants (58, 59), squid eyes have long provided a useful biochemical preparation to analyze the PLC/$InsP_3$ pathway (60-70). As described above, the retina is composed primarily of only one type of photoreceptor with no other neural cell type present, and with the outer segment of the photoreceptor facing the vitreous surface of the retina where they are readily accessible. Furthermore, cephalopod eyes are quite large and may provide considerable quantities of tissue, an advantage which has been first exploited to extract rhodopsin from squid, cuttlefish and octopus (71, 72) and to determine its amino acid sequence (73, 74). In this view, it is noteworthy that: 1) invertebrate rhodopsin is regarded as the prototypical member of the G-protein coupled receptors (GPCR) family (75) and 2) squid rhodopsin belongs to the restricted family of GPCR whose crystal structure has been reported (76), the other two being bovine rhodopsin (77) and human β_2-adrenergic receptor (78). Similar to other invertebrates, squid and octopus rhodopsin contains the 11-*cis*-retinal chromophore covalently bound to a lysine residue within its binding pocket. Light absorption induces chromophore photoisomerization to the all-*trans* species, which acts as an agonist and permits the onset of the phototransduction cascade (79). Active rhodopsin (the so-called "t-acid meta-rhodopsin") interacts with a heterotrimeric G protein (iG_q), resulting in GTP binding to $iG_{q\alpha}$, which in turn dissociates from $iG_{q\beta\gamma}$ and stimulates a 140 kD PLC (PLC-140) to hydrolyze phosphatidylinositol 4,5-bisphosphate (PIP_2) to $InsP_3$ and diacylglycerol (DAG) (5, 64, 69, 80, 81). In accordance with this model, in a preparation of squid outer segments, a light flash may increase $InsP_3$ levels by 200% (e.g. about 5 μM) and decrease PIP_2 content by 50% (69). The transduction pathway between rhodopsin and PLC provides several sites of regulation. The inactivation of visual signalling may result from: 1) the intrinsic GTPase activity of $iG_{q\alpha}$, which can be enhanced by fivefold by PLC-140 (64; see below); 2) rhodopsin phosphorylation by rhodopsin kinase (63); and 3) arrestin binding to rhodopsin (67), which is the rate-limiting step in both vertebrate and invertebrate phototransduction. Indeed, the latter process prevents further associations between t-acid meta-rhodopsin and iG_q and limits additional PLC activation (65). A recent study demonstrates that squid arrestin provides an additional target for rhodopsin kinase phosphorylation, although the physiological outcome of this interaction remains unclear (67). It is, however, conceivable that arrestin phosphorylation by rhodopsin kinase might contribute to desensitize the photoresponse (67). Two distinct isoforms of PLC have been purified from the cytosol of squid photoreceptors, namely PLC-140 (64, 82) and a 70 kDa PLC (PLC-70) (83). PLC-140 has been only found in squid eyes (82) and displays a remarkable similarity in structure and organization with the β family of mammalian PLC (64), which is regulated by G proteins α subunits (84). Accordingly, PLC-140 shares a 39-40% identity with PLC-β1 and PLC-β4, and a 36-39% identity with PLC-β3 and PLC-β4 (64). Moreover, PLC-140 structure encompasses six distinct domains that have been also found in mammalian PLC-β subtypes: N-terminal pleckstrin homology (PH), which mediates PLC anchoring to membrane phosphoinositides, X and Y catalytic, G- and P-boxes, and C-terminal C2, which is responsible for intracellular Ca^{2+} sensing (64; see below). Accordingly, PLC-140-dependent PIP_2 hydrolysis is maximal at 1 μM Ca^{2+} (82), a feature in accordance with the Ca^{2+}-sensitivity of all PLC isozymes (83). Nevertheless, PLC-140 lacks the EF-domain, which aids C2 in detecting intracellular Ca^{2+} (83). Similar to PLC-140, the partial amino acid sequence of PLC-70 displays homology with the mammalian PLC-β isoforms, and its PIP_2-hydrolising activity is regulated by $G_{q\alpha}$ proteins (83). However, PLC-70 is functionally distinguished from PLC-140 by its differential sensitivity to Ca^{2+}, the former being maximally activated at 100 μM Ca^{2+} (EC_{50}≅0.5 μM) (83). Such a feature might hint at the distinct roles played by the two isozymes in decoding light information by cephalopod photoreceptors. The reciprocal interaction between $iG_{q\alpha}$ and PLC-140 suggests that PLC-140 is the primary molecular target engaged upon rhodopsin stimulation. Accordingly, this enzyme is in the right position to control both the onset (it is turn on by $iG_{q\alpha}$) and the end (its GTPase activity limits the activity of its own stimulator) of the phototransduction process (see also 85). Subsequently, the presumed increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) occurring after PLC-140 recruitment might activate PLC-70 (83) and provide a positive feed-back to sustain the phototransduction cascade. It is worth noting that $iG_{q\alpha}$ might augment PLC-70 sensitivity to Ca^{2+} and, thus, allow the phospholipase engagement at Ca^{2+} levels lower than the high micromolar range (83). Although the biochemical steps leading to the engagement of both PLC subtypes have been firmly established, and both isozymes are considered essential to raise $[Ca^{2+}]_i$ and depolarize photoreceptor membrane upon light absorption, there are no reports on light-elicited elevation in $[Ca^{2+}]_i$ in cephalopod

rhabdomeres. In addition, the "whole-cell" patch clamp analysis of the evoked photocurrent has been rather scarce (50, 86; see Paragraph 5). In most invertebrates, including *Limulus* and *Drosophila melanogaster*, excitation of rhabdomeric photoreceptors is accompanied by a large intracellular Ca^{2+} signal. Indeed, whereas light-induced depolarization serves to deliver the visual input to the CNS, the parallel increase in $[Ca^{2+}]_i$ is responsible for the pronounced light adaptation (87-90), i.e. the mechanism whereby rhabdomeres may adjust their sensitivity to the average light level they encounter (91). The elevation in $[Ca^{2+}]_i$ results from $InsP_3$-dependent Ca^{2+} release from the endoplasmic reticulum underlying the microvillar membrane and Ca^{2+} influx from extracellular space (90). The relative contribution of both sources to the overall Ca^{2+} signal is variable from species to species: $InsP_3$-induced Ca^{2+} release is necessary for generating the entire light response of *Limulus* ventral photoreceptors (90), while Ca^{2+}-inflow through transient receptor potential (TRP) and TRP-like Ca^{2+}-permeable channels predominates in *Drosophila melanogaster* photoreceptors (52; but see 92). The following pieces of evidence suggest an increase in intracellular Ca^{2+} levels within cephalopod photoreceptors upon exposition to light: 1) $InsP_3$ concentration increases both in *in vitro* and *in vivo* preparations (68, 69); 2) arrestin phosphorylation by rhodopsin kinase requires the presence of Ca^{2+} (67); 3) PIP_2 hydrolysis by PLC-70 is maximally enhanced by 100 μM Ca^{2+} (but see above), a value which has been measured in photoactivated *Drosophila* photoreceptors (93); and 4) PLC-140 may be cleaved into a 95 kDa PLC and a 35 kDa fragment by a Ca^{2+}-dependent protease, most likely calpain (94). The experimental evidence of light-elicited intracellular Ca^{2+} signalling in cephalopods will likely benefit from studies on enzymatically isolated squid photoreceptors, which represent an attractive model system to investigate visual processes at physiological level (86). A recent paper has described an exciting, novel function for $InsP_3$ signalling in cephalopod rhabdomeres. $InsP_3$ has been shown to bind to squid rhodopsin, PLC-140 and rhodopsin kinase with individual affinities (62), which suggests that phosphatidylinositol turn-over exerts feedback effects on upstream steps in light-elicited signal transduction cascade. Importantly, other hitherto unidentified proteins within cephalopod visual system might exhibit $InsP_3$-binding properties (62). The nature (positive or negative) of these feedbacks is still unclear, however, it indicates that, as well as Ca^{2+} and cyclic AMP (11), $InsP_3$ microdomains might affect distinct subcellular processes depending on the molecular targets residing within its production site (see also 95).

6. IS THERE A ROLE FOR TRP CHANNEL IN LIGHT-INDUCED RHABDOMERE DEPOLARIZATION IN CEPHALOPODS?

A novel tissue slice preparation obtained from the retinas of very young cuttlefish (*Sepia officinalis*) has recently provided valuable insights into the cephalopod light-induced current (LIC) (50). The "whole-cell" patch-clamp analysis performed on this preparation has shown that LIC displays a current-to-voltage (IV) curve reversing between 0 and +20 mV (50), which indicates a non-specific cation conductance, similar to that found in *Drosophila* photoreceptors (0/+40 mV) (96). The Ca^{2+}/Na^{+} permeability ratio, whose value amounts to 100:1 in the fruit fly (52), however, has not been determined. As suggested by the IV-relation shape, cuttlefish photocurrents are inwardly directed at a holding membrane potential of -60 mV and are, thus, depolarizing (50). The LIC is prevented either by inhibiting PLC and $InsP_3Rs$ or by the application of DAG surrogates (50). These findings confirm that phototransduction process in cephalopods impinges on both branches of PLC-dependent signalling. The molecular route for the depolarizing photocurrent is likely to be provided by a 92 kDa protein, whose amino acid sequence is homologous to the product of the *Drosophila* TRP gene and has, thus, been termed sTRP (squid homolog of *Drosophila* TRP gene) (5, 97). In the fruit fly photoreceptors, TRP channels, either alone or in combination with TRP-like channels, underlie the LIC that produces the photoreceptor potential and the sensation of light (93, 98). The discovery of sTRP in squid rhabdomeres does not itself imply that such a protein either mediates or contributes to LIC in cephalopods. Molecular ablation of the 92 kDa channel by using the small interference (siRNA) technique will likely provide more reliable insights into its role in light-induced photoreceptor depolarization. The mechanism whereby the photocurrent is activated in cephalopods is also largely unclear. According to a popular model, opening of *Drosophila* TRP channels required the previous depletion of intracellular Ca^{2+} stores, a mechanism universally known as store-operated calcium entry (SOCE). However, more recent work has demonstrated that store emptying is not responsible for TRP channel gating in *Drosophila* rhabdomeres: evidence is mounting that either DAG or its metabolites, such poly-unsaturated fatty acids (PUFA), might be responsible their activation in this system (93, 98). Nevertheless, according to the results obtained by Chrachri, the cephalopod photoreceptors LIC is inhibited by the application of DAG surrogates (50). In light of the diverse mechanisms which underlie TRP channels gating in mammals (99), and of the observations reported in cuttlefish (50), it is conceivable to envisage one of the following mechanisms to operate in cephalopods: 1) sTRP directly interacts with intracellular $InsP_3Rs$ and channel activation is mediated through coupling to $InsP_3Rs$ (100); 2) sTRP belongs to the group of the hitherto unidentified $InsP_3$-binding proteins and is directly activated by such phosphoinositide; and 3) sTRP is inhibited by PIP_2 in the dark, while light-induced PLC stimulation leads to phosphoinositide depletion and relieves the channel from PIP_2-dependent block (101; see also 102). The former hypothesis is ruled out by the observation that squid $InsP_3Rs$ do not physically couple with the TRP channel (5). Conversely, the second option is supported by the reported LIC inhibition by heparin (50), which competes with $InsP_3$ for binding sites on $InsP_3Rs$ (103). Interestingly, the ability of squid PLC-140 to bind to the C-terminal domain of rhabdomeric sTRP (5) places the phospholipase in the most suitable position to rapidly gate the channel by either synthesizing $InsP_3$ (model #2) or simply hydrolyzing PIP_2 (model #3). In this context, it worth noting that both

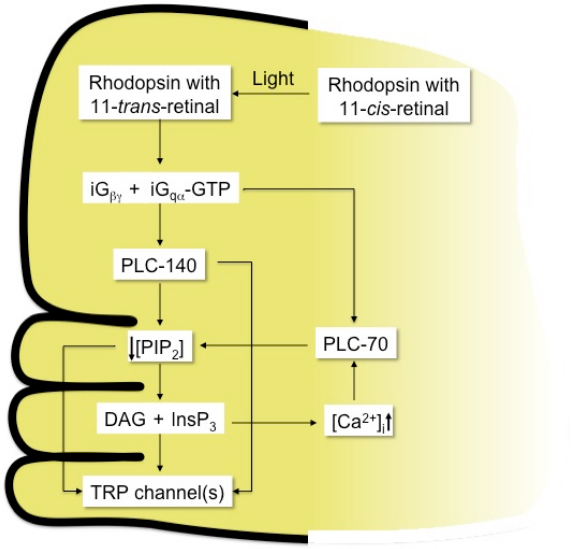

Figure 2. Diagram of the light-induced signalling cascade leading to the increase in [Ca2+]i and to TRP channels stimulation. The model represents the putative model whereby light-induced photoisomerization of rhodopsin to the all-*trans*-species results in the elevation in intracellular Ca2+ levels and in the TRP channel(s) opening. See the text for the full description of the pathways recruited by **t-acid meta-rhodopsin.**

vertebrate and invertebrate cells assemble proteins of a particular signalling pathway into multimolecular complexes to achieve signalling specificity and speed up biochemical processes (104). The core of such signal complexes is the multi-PDZ scaffold protein INAD, whose genetic ablation strongly suppresses *Drosophila* photocurrent (98; but see 83). INAD is missing in squid rhabdomeres (5), however, its function might be fulfilled by the direct interaction between PLC-140 and sTRP. In vertebrates, the formation of an inter-molecular non-canonical PH domain between PLC-γ, which is activated by tyrosine kinase receptors, and canonical TRP channel 3 (TRPC) control channel trafficking and cell-surface expression (105). Non-canonical PH domains are likely conserved throughout evolution within the different members of the PLC family and could play a pivotal role in the regulation of physiological processes (105). Therefore, it would be worth testing the hypothesis that an inter-molecular PH domain underlies the physical coupling between PLC-140 and sTRP. Light onto the variety of mechanisms which we have proposed might only be shed by further electrophysiological analysis of LIC. More specifically, single-channel recordings from excised rhabdomere membranes combined to a detailed pharmacological/molecular approach should significantly advance our knowledge of the signalling system leading to the onset of the photocurrent. A tentative model of the mechanisms leading to LIC activation, as well as to the increase in intracellular Ca^{2+} levels, is depicted in Figur e 2.

7. PERSPECTIVES

Cephalopods have long provided ideal cellular systems to gain more insights into vertebrate physiology. Not only the elucidation of the ionic bases of action potentials and of the Ca^{2+}-requirement of neurotransmitter release has been firmly established due to the easy handling of squid giant synapse. Following the discovery of $InsP_3$ as an intracellular second messenger, squid rhabdomeres have represented one of the most suitable systems to investigate the biochemical cascade upstream of its production and to detect physiologically relevant increases in its concentration. It is, therefore, surprising that the signalling events downstream of its synthesis are still mist-shrouded. In our opinion, future investigation on light-activated intracellular pathways in cephalopod photoreceptors will help to unravel the following issues: 1) Is there an increase in $[Ca^{2+}]_i$ upon rhodopsin stimulation? If yes, which is the relative contribution of intracellular Ca^{2+} release *vs.* extracellular Ca^{2+} entry? 2) Which is (are) the role(s) of the Ca^{2+} bout? 3) In the context of the point #2, is it possible to modulate light-induced Ca^{2+} elevation by neuromodulators/neurotransmitters released by the afferent fibers incoming to the retina from the optic lobe? For instance, it has been shown that pigment migration, which occurs during light/dark adaptation and is controlled by intracellular Ca^{2+} levels (90), is differently regulated by dopamine and FMRFamide (48, 49). Since both agonists may cause an increase in $[Ca^{2+}]_i$, do these aminergic transmitters impact on light-elicited signaling? In other words, do the visual system display a form of plasticity inherent to its network properties (i.e., the interplay between eye and optic lobe); 4) Is sTRP the sole protein channel responsible for the photocurrent (unlikely) or is aided in this task by other TRP isoforms or other yet to identify proteins? 5) Which is the molecular mechanism responsible for the gating of light-regulated channels? Providing a clear-cut answer to such questions is not trivial, since eyes supply cephalopods with a plethora of information that drive the complex behavior of these animals, which are by far more complex and potentially more indicative of vertebrate –like activity than any other invertebrates currently under investigation (1, 20). In this view, the analysis of the sub-cellular machinery activated by light in cephalopod photoreceptors might shed light also on biochemical processes still unknown in mammals. The following evidence certainly deserves a more careful investigation, not only in cephalopod rhabdomeres, but also in mammalial cells: 1) Arrestin phosphorylation by rhodopsin kinase: this feature places arrestin in the family of the substrates of G-protein coupled receptors kinases, including also tubulin and ezrin (see Discussion in 67). Whether this mechanism is involved in the desensitization of the visual signal transduction, both in invertebrates and vertebrates, needs to be further explored. 2) $InsP_3$-binding to a variety of proteins involved in the visual transduction cascade, such as PLC-140, rhodopsin and rhodopsin kinase. The plethora of functions regulated by Ca^{2+} mobilized through $InsP_3Rs$ on ER membranes rightly led researchers worldwide to focus their efforts on unraveling the role of $InsP_3$ in intracellular Ca^{2+} dynamics. A minor number of investigations, however, have demonstrated that $InsP_3$ may

bind to targets other than $InsP_3Rs$, notably PLC-δ1 and PRIP-1 and -2 (PLC-related, but catalytically inactive protein) (106). While PRIP-1 serves as a molecular cargo shuttling $InsP_3$ from the subplasmalemmal space (where it is synthesized) to ER (where it opens $InsP_3Rs$), PRIP-2 may modulate GABA signalling upon binding to the β-subunit of $GABA_A$ receptors (106). It, thus, appears that the range of intracellular processes either directly or indirectly modulated by $InsP_3$ is far more intricate than previously thought and cephalopod rhabdomeres might well aid in shedding more light on such issue. 3) The physical coupling between PLC-140 and sTRP suggests that, along with the γ-isoform, PLC-β might interact with TRP channels also in vertebrate cells. Correct trafficking of TRPC3 channels to the plasma membrane is controlled by PLC-γ and is essential to mediate agonist-induced Ca^{2+} entry (105). It is tempting to speculate that distinct pools of plasmalemmal TRP are engaged by different receptors (either G-proteins coupled or tyrosine kinase receptors) in order to promote diverse signalling pathway within the cells.

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Send correspondence to: Francesco Moccia, Department of Structural and Functional Biology, University of Naples, Federico II, Complesso Universitario Monte S. Angelo, Viale Cinthia, 80126 Naples, Italy, Tel: 39-081-679-075, Fax: 39-081-679-233, Email: moccia1972@hotmail.it

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