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REVIEW ARTICLE

Understanding the dermal light sense in the context of integrative photoreceptor cell biology

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Abstract

While the concept of a dermal light sense has existed for over a century, little progress has been made in our understanding of the mechanisms underlying dispersed photoreception and the evolutionary histories of dispersed photoreceptor cells. These cells historically have been difficult to locate and positively identify, but modern molecular techniques, integrated with existing behavioral, morphological, and physiological data, will make cell identification easier and allow us to address questions of mechanism and evolution. With this in mind, we propose a new classification scheme for all photoreceptor cell types based on two axes, cell distribution (aggregated *vs.* dispersed) and position within neural networks (first order *vs.* high order). All photoreceptor cells fall within one of four quadrants created by these axes: aggregated/high order, dispersed/high order, aggregated/first order, or dispersed/first order. This new method of organization will help researchers make objective comparisons between different photoreceptor cell types. Using integrative data from four major phyla (Mollusca, Cnidaria, Echinodermata, and Arthropoda), we also provide evidence for three hypotheses for dispersed photoreceptor cell function and evolution. First, aside from echinoderms, we find that animals often use dispersed photoreceptor cells for tasks that do not require spatial vision. Second, although there are both echinoderm and arthropod exceptions, we find that dispersed photoreceptor cells generally lack morphological specializations that either enhance light gathering or aid in the collection of directional information about light. Third, we find that dispersed photoreceptor cells have evolved a number of times in Metazoa and that most dispersed photoreceptor cells have likely evolved through the co-option of existing phototransduction cascades. Our new classification scheme, combined with modern investigative techniques, will help us address these hypotheses in great detail and generate new hypothesis regarding the function and evolution of dispersed photoreceptor cells.

Keywords: Extraocular photoreceptors, Non-visual photoreception, Evolution, Phototransduction, Invertebrates

Introduction

Light infiltrates almost every environment on Earth and strongly impacts most animals' lives. Animals detect light using sensors known as photoreceptor cells. Photoreceptor cells are best known from the retinas of animal eyes, but they are also found outside the eyes, where they are often called "extraocular photoreceptor cells" (EOPCs). EOPCs are found in both eyed and eyeless animals, and in some cases, they confer a particular form of photoreception known as the "dermal light sense." Millott (1968) defined the dermal light sense as a "widespread photic sense that is not mediated by eyes or eyespots and in which light does not act directly on an effector." How is the dermal light sense employed by animals? Do the same biochemical and physiological mechanisms underlie the dermal light sense in all animals? How are the photoreceptor cells that confer the dermal light sense related to the photoreceptor cells found in animal eyes? Answering these and other questions requires knowledge about the structure and function of the dermal light sense in a wide variety of animals.

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Unfortunately, our understanding of the dermal light sense has not progressed much since Millott's (1968) work; it is clear that we still know relatively little about this form of light perception. Although we have identified many behaviors that may be mediated by a dermal light sense, in most cases, we have not identified the primary sensory cells and/or biochemical pathways involved in these behaviors. Additionally, we know that many animals possess eyes, extraocular photoorgans, and perhaps also "dermal" photoreceptor cells, but we often do not understand how the separate contributions of these specific systems or photoreceptor cell types relate to particular behaviors. In fact, the term *dermal light sense* may itself be misleading, as it is unclear if the receptors that confer this sense are located at or directly below the skin surface. Finally, we rarely know how many receptors are involved in the dermal light sense, how these receptors are distributed in space, or whether these receptors are primary sensory cells (like retinal photoreceptor cells) or fine processes extending from higher-order neurons (Kennedy, 1960; Wiederhold et al., 1973).

Despite a wealth of unanswered basic questions regarding dermal photoreceptor cell identity and function, recent advances in our understanding of the molecular basis of phototransduction offer new ways to study and understand the dermal light sense. Thus, we have three goals for this paper. First, we will clarify the

meaning of the dermal light sense by providing a new classification scheme for all photoreceptor cells. Next, we will present data related to the following three hypotheses about dispersed photoreceptor cells: a) that they are involved in behavioral tasks that do not require true spatial vision (i.e., the ability to form images); b) that they do not express morphological features that enable retinal photoreceptor cells to maximize light gathering power or restrict the direction from which light is collected, such as expanded membrane surface areas or pigmentation, respectively; and c) that dermal light senses have evolved a number of times in animals, and, in some instances, may have originated through the co-option of existing phototransduction pathways. Finally, we will discuss the implications our hypotheses hold for the evolution of dermal light photoreceptor cells and illustrate how detailed comparisons between objectively categorized photoreceptor cells deepen our understanding of the evolution of photosensory systems in general.

(Re)defining the dermal light sense

A first goal for this review is to outline a new classification scheme for photoreceptor cells that relies on both a receptor's anatomical distribution within an animal (e.g., dispersed or aggregated) and its position within a neural network (e.g., primary/first order or higher order). A new and objective way to group photoreceptor cells is necessary to make more meaningful comparisons between different cells. We have purposely excluded other methods of receptor classification from our scheme because they often do not apply to the cells conferring the dermal light sense and may rarely apply to EOPCs in general. One such method of classification divides receptors by the types of information that they gather about light, for example, temporal (changes in light intensity over time), directional (differences in intensity in a gradient), or spatial (true image formation). Furthermore, these types of information are also often thought to be linked to particular structures or photo-organs; for example, it is thought that spatial vision is generally restricted to eyes (however, see "Hypothesis I" in the section titled "Hypotheses and data for dispersed photoreception"). Photoreceptor cells have also been traditionally categorized as either ciliary or rhabdomeric (*sensu* Eakin, 1972), but dermal photoreceptor cells often do not possess either of these types of morphological modification (but, see "Hypothesis II" in the section titled "Hypotheses and data for dispersed photoreception"). We believe that the characters we have chosen, distribution and neural identity, can be used to describe a wider set of light sensitive neurons than these prior classification schemes. By explicitly defining the photoreceptor cells that confer the dermal light sense, we will be better able to explore functional and evolutionary differences and similarities between receptor cell types and propose specific hypotheses regarding the origin and evolution of dermal light sense photoreceptor cells.

We propose that all photoreceptor cells can be classified using two axes (see Fig. 1), provided that we rely on characters of the photoreceptor cells themselves and not on characters of the organs to which these cells might belong. The first axis in our classification scheme is continuously varying and describes the extent to which photoreceptor cells are dispersed or aggregated on the surface of an animal's body. While elaborating specific details is beyond the scope of the current contribution, we propose that this "dispersed *versus* aggregated" axis should be fully quantifiable using spatial point pattern statistics (e.g., Diggle, 2003). For example, a null model in spatial statistics is complete spatial randomness (CSR), and departures from CSR can occur by aggregation or dispersion (repulsion). We imagine that photoreceptor cell distribution patterns can thus be quantified on a continuous axis, ranging from highly aggregated to highly dispersed. In addition, whether photoreceptor cells are aggregated or dispersed could be the subject of discrete statistical tests. Photoreceptor cells that are relatively close together, like those in eyes, are strongly aggregated. In contrast, other photoreceptor cells may be dispersed across the surface of an animal's body and rarely occur next to each other. Some photoreceptor cells, like the paired pigmented cells used for directional photoreception in animals such as acoel worms or the receptors associated with the eyespots of some spiralians, will likely be statistically indistinguishable from CSR and will be neither statistically aggregated nor dispersed. Classifying photoreceptor cells by the extent of their dispersion also offers a more quantitative definition of what constitutes an eye. For example, eyes can be described as collections of aggregated photoreceptor cells that provide spatial vision (Land & Nilsson, 2002).

The second axis in our classification scheme has two discrete states that identify receptors as either first- or higher-order neurons. First-order neurons are primary sensory cells that transduce external stimuli into electrical signals, then pass these signals onto other neurons via synapses. Classic retinal photoreceptor cells, like rods and cones in the vertebrate eye, fit this description. While the best-characterized photoreceptor cells are first-order neurons, higher-order neurons can also be light sensitive. These higher-order neurons (or "interneurons") have many synaptic connections with other neurons and can both send and receive electrical signals. Many higher-order neurons do not directly receive sensory stimuli from outside the animal. Nevertheless, photoreceptive interneurons have been described in a wide range of animals: examples include ipRGCs in vertebrates (Provencio et al., 2000), certain neural tissues in mammals (Tarttelin et al., 2003), abdominal ganglia in the gastropod molluscs *Aplysia* (Arvanitaki & Chalazonitis, 1961) and *Onchidium* (Hisano et al., 1972*a*), and abdominal ganglion cells in arthropods such as crayfish (Kennedy, 1960) and lobsters (Wilkens & Larimer, 1972).

Taken together, these two axes for receptor classification produce four separate quadrants (Fig. 1). As described in the preceding paragraphs, photoreceptor cells can fall into one of two distinct categories of neural identity on the *y*-axis, either first order or higher order, and can vary continuously in their amount of dispersion on the *x*-axis. Quadrant I contains aggregated high-order neurons, such as those found clustered in ganglia from the marine gastropod *Onchidium* (Hisano et al., 1972*a*) and the crayfish *Procambarus clarkii* (Kennedy, 1963). These receptors tend to be morphologically similar to the other neurons in the ganglia where they occur. Quadrant II houses dispersed high-order neurons. Curiously, we have yet to identify any examples of photoreceptor cells that are both dispersed and higher order. Quadrant III houses aggregated first-order neurons typified by the retinal photoreceptor cells used for image formation in many animal eyes. This quadrant also contains the photoreceptor cells found in well-characterized extraocular photo-organs like frontal organs/parietal eyes in non-mammalian vertebrates and parolfactory glands/epistellar bodies in cephalopods. These cells are aggregated first-order neurons that often bear classic retinal photoreceptor cell morphologies (reviewed in Nishioka et al., 1962, 1966; Adler, 1976). Finally, Quadrant IV contains cells that are dispersed first-order neurons. We argue that the receptors that confer the dermal light sense belong in this fourth quadrant. As we are primarily interested here in defining and studying the dermal light sense, the remainder of this review will

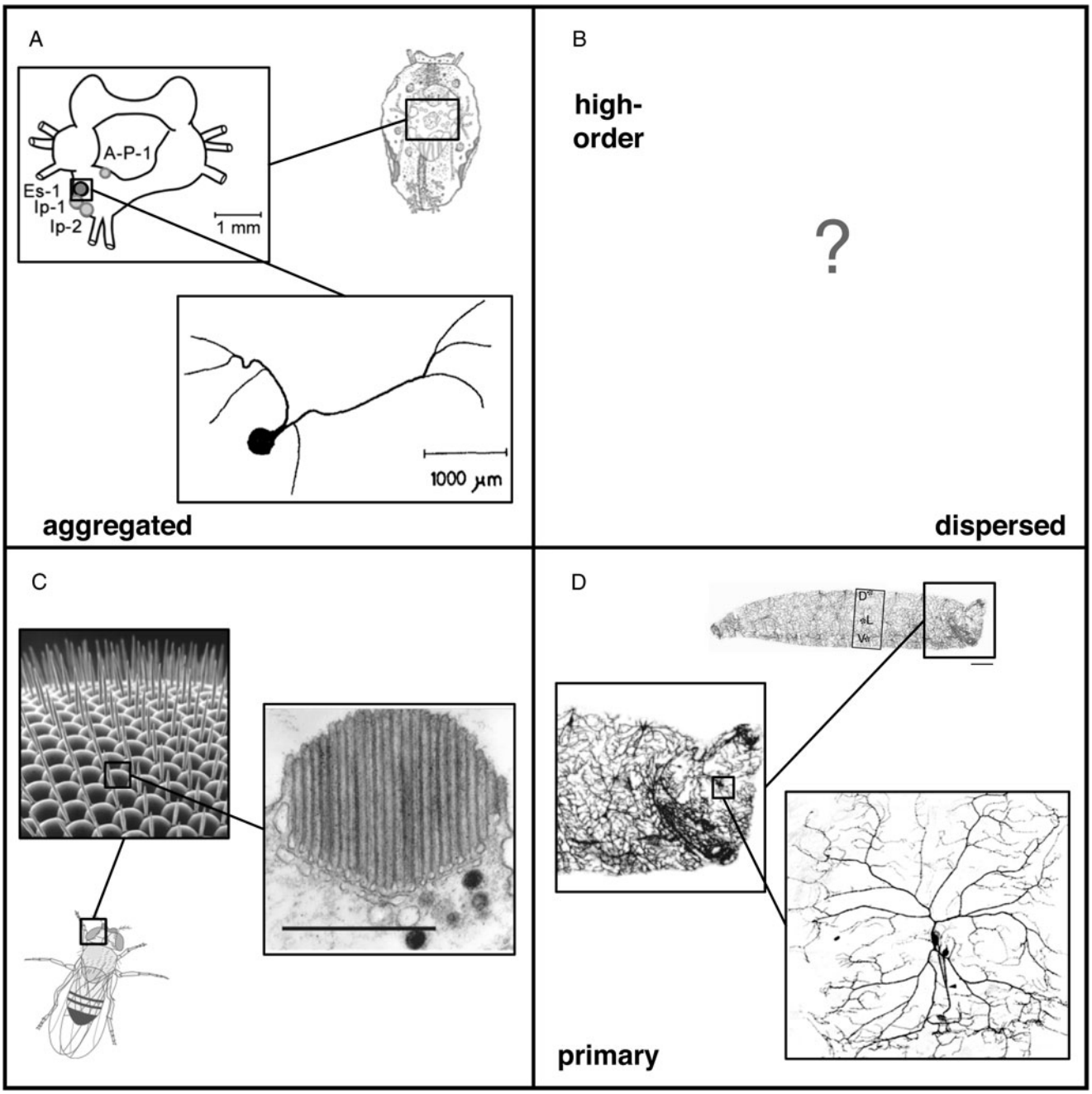

Fig. 1. Photoreceptor cell distributions and neuron types. Photoreceptor cell distribution ranges from aggregated to dispersed on the x-axis. Photoreceptor cell type is either primary or higher-order neuron on the y-axis. (A) Drawing of Onchidium verruculatum, abdominal ganglion with photosensitive neurons Ip-1, Ip-2, Es-1 and A-P-1, and morphology of neuron Es-1 (adapted with permission from Springer Science & Business Media: Journal of Comparative Physiology A: Neuroethology, Gotow, 1975; Gotow & Nishi © Rockefeller University Press, 2002. Originally published in Journal of General Physiology. 120:581-597. doi:10.1085/jgp.20028619). (B) No example of this type of photoreceptor cell. (C) Illustration of Drosophila melanogaster, micrograph of compound eye and micrograph of single rhabdomere within eye ommatidia. Scale bar, 1 μm (from Mrabet, 2008; Howard, 2008 and adapted by permission from MacMillan Publishers Ltd.: Nature, Hardie & Raghu, 2001). (D) Illustration of D. melanogaster larvae (Scale bar, 200 μm), class IV dendritic arborization neurons tiling the body wall, confocal image of a single class IV dendritic arborization neuron (adapted with permission from Development, Grueber et al., 2002; adapted with permission from MacMillan Publishers Ltd.: Nature, Xiang et al., 2010).

focus solely on these dispersed primary sensory cells. Henceforth, we will refer to these cells as "dispersed photoreceptor cells," part of a "dispersed" photoreception system and avoid the less specific terms "dermal" and "dermal light sense." Dispersed first-order neurons in Quadrant IV are typified by the sensory neurons that tile the body wall of *Drosophila melanogaster* larvae (Xiang et al., 2010). More examples of dispersed photoreceptor cells may be found in Table 1.

Finally, we present three notes concerning the scope of this review. a) Although many larval photo-organs and photoreceptor

Table 1. *Types of photoreceptor cells found in different metazoan phyla*

Taxon	Photoreceptive tissue	Photoreceptor quadrant	Photoreceptor ultrastructure *sensu* Eakin	Photoreceptor neurophysiology	Phototransduction components	References
Cnidaria						
Medusazoa	Rhopalia/ocelli	III	Ciliary	—	Cnidopsin, Gs, CNG	Yamasu and Yoshida (1973); Suga et al. (2008); Kozmik et al. (2008); Koyanagi et al. (2008)
	Planula	III	Rhabdomeric	—	—	Nordstrom et al. (2003)
	Epithelial cells	IV	Neither	—	Cnidops, Arrestin, CNG	Haug (1933); Eakin and Westfall (1962); Rushforth et al. (1963); Yamasu and Yoshida (1973); Singla (1974); Plachetzki et al. (2007, 2009); Suga et al. (2008)
Echinodermata	Armtip ocelli, Tentacular eyespots	III	Rhabdomeric (*Asterias*) both (*Henricia*)	—	—	Cobb and Moore (1986); Cobb and Hendler (1990); Johnsen (1997)
	Dispersed photoreceptor cells	IV	—	—	c-opsin, r-opsin?, Go-opsin?	Woodley (1982); Aizenberg et al. (2001); Burke et al. (2006); Raible et al. (2006); Rubin et al. (2006); Yerramilli and Johnsen (2010); Ooka et al. (2010)
Cephalochordata	Dorsal pigmented ocelli (organs of Hesse), Frontal eye-Lamellar bodies	III	Rhabomeric (ocelli) Ciliary (lamellar bodies, frontal eye)	Depolarizing (*ocelli*)	Peropsin, r-opsin, c-opsin	Eakin and Westfall (1962); Ruiz and Anadon (1991); Koyanagi et al. (2002, 2005); Nasi & Gomez (2009)
	Joseph cells	IV	Rhabdomeric	Depolarizing	—	Lacalli (2004); Eakin and Westfall (1962); Del Pilar Gomez et al. (2009)
Urochordata	Larval ocellus, Siphon eyespots	III	Ciliary (larval) Rhabdomeric (adult)	Hyperpolarizing	c-opsin, Gi	Eakin (1972); Dilly and Wolken (1973); Kusakabe et al. (2001); Kusakabe and Tsuda (2007)
Vertebrata	Rods & cones, Pineal eyes, Parietal eyes	III	Ciliary	Hyperpolarizing	c-opsin, Gt, PDE, CNG	Eakin (1961); reviewed in Fu et al. (2007) reviewed in Mano and Fukada (2007)
	ipRGCs, Frontal organ	III	Neither	Depolarizing	r-opsin, Gq, PLC, TRP	Panda et al. (2002); Hattar et al. (2003)
	Chromatophores	IV	—	—	—	Bagnara and Obika (1967); reviewed in Oshima (2001)
Nematoda	ASJ, AWB, ASK and ASH neurons (*C. elegans*), Ganglionic photoreceptors	I	Neither	Hyperpolarizing	lite-1, Gi/o, CNG	Ward et al. (2008); Edwards et al. (2008); Liu et al. (2010)
	Ocelli, amphid photoreceptors	III	Rhabdomeric, ciliary	—	—	Hyman (1951); Siddiqui and Vigglierchio (1970)

Table 1. Continued.

Taxon	Photoreceptive tissue	Photoreceptor quadrant	Photoreceptor ultrastructure *sensu* Eakin	Photoreceptor neurophysiology	Phototransduction components	References
Arthropoda	Caudal photoreceptors	I	Neither	Depolarizing	—	Kennedy (1963); Wilkens and Larimer (1972)
	Larval ocelli/stemmata/bolwigs, Adult eyes, Genital photoreceptors	III	Rhabdomeric	Depolarizing	r-opsin, Gq, PLC, TRP	Bolwig (1946); Arikawa and Miyako-Shimazaki (1996); Eakin (1972); reviewed in Hardie (2001)
	Larval ddaC neurons	IV	Neither	—	Gr28b, TRPA1	Xiang et al. (2010)
Platyhelminthes	Epidermal cells	IV	Neither		—	Eakin (1972); Dörjes (1968)
	Ocelli	III	Rhabdomeric		—	Eakin (1968)
Annelida	Larval brain	I	—	—	c-opsin	Arendt et al. (2004)
	Cephalic eyes	III	Rhabdomeric	—	r-opsin	Arendt et al. (2004)
Mollusca	Phaosomes	IV	Neither	—	—	Rohlich et al. (1970)
Polyplacophora	Aesthete eyes	III	Rhabdomeric	—	—	Boyle (1969)
	Girdle	IV	—	—	—	Arey and Crozier (1919)
	Larval epithelium	IV	—	—	—	Heath (1904)
Cephalopoda	Eyes, Epistellar ganglia, Parolfactory vesicles, Photophore	III	Rhabdomeric	Depolarizing	r-opsin, Gq, PLC, TRP	Nishioka et al. (1966); Mauro (1977); Cobb et al. (1995); Cobb and Williamson (1998*a*,*b*) Hara and Hara (1980); Tong et al. (2009)
	Skin	IV	—	—	r-opsin	Mathger et al. (2010)
Bivalvia	Mantle eyes, Siphonal eyes	III	Rhabdomeric, ciliary	Hyperpolarizing, depolarizing	r-opsin, Go-opsin, Gq, Go, PLC, TRP, CNG	Barber and Wright (1969); Nilsson (1994); Kojima et al. (1997); Gomez & Nasi (2000)
	Phaosomes (siphon)	IV	Neither	—	—	Kennedy (1960)
Gastropoda	Oesophageal ganglia	I	Neither	Both	Gp, Gt, PDE, cGMP	Hisano et al. (1972*b*); Gotow and Nishi (2008)
	Dorsal ocelli	III	Ciliary	—	—	Yanase and Sakamoto (1965)
	Cephalic eyes	III	Rhabdomeric, ciilary (Heteropoda)	Depolarizing	r-opsin, Gq, PLC, TRP	Eakin and Brandenburger (1967); reviewed in Salvini-Plawen and Mayr (1977); Sakakibara et al. (2005); Chrachri and Nelson (2005)
	Dermis	IV	—	—	CNG	Zylstra (1971), Pankey et al. (2010)

cells can be included in our classification scheme, for space considerations, we are restricting our review to photoreceptor cells found in adult metazoans. b) For this review, we define photoreceptor cells as the neurons that convert light into an electrical signal via a signal transduction cascade (per Richter et al., 2010). This definition restricts our discussion to neural cells; however, we must note that there are other types of cells that also transduce light. Instead of relaying an electrical signal, this type of cell, called an effector cell, most often converts light directly into mechanical energy. For example, the alga *Chlamydomonas* uses light-sensitive ion channels (channelrhodopsin-1 and -2) to directly drive the flagellar beating responsible for positive and negative phototaxis (reviewed in Hegemann, 2008). It is worthwhile to consider the functions and evolution of effector cells, but for the purpose of this review, we will not consider them further. c) Finally, we will not discuss other photopigments besides opsins, like cryptochromes. It is well known that cryptochromes mediate circadian rhythms in many organisms and can be found in numerous cell types (reviewed in Cashmore et al., 1999). However, while cryptochromes are clearly associated with EOPCs, these cells are usually aggregated higher-order cells, and not dispersed photoreceptor cells, and are thus beyond the scope of this review.

The molecular basis of photoreceptor function

Although our understanding of dispersed photoreception may have changed little since 1968, enormous progress has been made toward understanding the biochemical and molecular basis of light sensitivity in animals. This molecular synthesis has facilitated deeper insights into photoreceptor cell morphology, physiology, and evolution (Arendt, 2003). While the molecular synthesis was forged primarily from data on retinal photoreceptor cells, we assume here that all photoreceptor cells, including those underlying dispersed photoreception, may be considered within the same framework. This perspective generates testable hypotheses about the genetics and physiology of dispersed photoreception and provides the potential for a more unified understanding of the evolution of all photoreceptor cells in animals (see Table 1).

Photoreceptor cells can be categorized by the degree of similarity between the molecular components that make up their phototransduction cascades. Phototransduction begins with a photon of light being absorbed by a visual pigment that consists of a chromophore (often the vitamin A derivative retinal) bound to a seven transmembrane domain G-protein coupled receptor known as an "opsin." Metazoan opsins appear to be monophyletic and to have originated before the common ancestor of Cnidaria-Bilateria (Plachetzki et al., 2007; Suga et al., 2008). Based on recent reconstructions of opsin phylogeny, opsins can be categorized into four separate clades defined by the G-protein with which they interact. The resulting categories include Gt-opsins, Gq-opsins, Gs-opsins, and Go-opsins. The well-characterized Gt- and Gq-opsins are generally found in cells with ciliary or rhabdomeric morphology, respectively, and are thus often referred to as "c-opsins" and "r-opsins" (Arendt & Wittbrodt, 2001). A third clade, the Gs-opsins (or "cnidops") is known only from cnidarians. The fourth clade includes Go-opsins, which were first discovered in scallop ciliary photoreceptor cells (Kojima et al., 1997). Although relatively poorly known, other Go-opsins have been found in lizard parietal eyes (Su et al., 2006), amphioxus ocelli (Koyanagi et al., 2002), and mammalian neural tissue (Tarttelin et al., 2003). Furthermore, genomic surveys indicate that Go-opsins may be found across Metazoa (unpublished observation).

The four opsin clades are each associated with distinct sets of downstream secondary messengers and ion channels. For example, Gt-opsins activate transducin, which signals through a cyclic nucleotide second messenger that closes cyclic nucleotide gated (CNG) ion channels (Fu & Yau, 2007). In contrast, Gq-opsins involve the secondary messenger inositol triphosphate that leads to intracellular calcium release and the opening of transient receptor potential cation (TRPC) channels (Hardie, 2001). In a box jelly, the Gs-opsin cascade involves adenylate cyclase (AC) (Koyanagi et al., 2008), and in the hydrozoan *Hydra*, a closely related opsin co-localizes with CNG (Plachetzki et al., 2010). Finally, although the majority of known photoreceptor cells use opsin-based phototransduction cascades, other methods of light detection exist. For example, lite-1 and its homologue, Gr28b, are light-sensitive gustatory receptors in *Caenorhabditis elegans* and *D. melanogaster*, respectively (Edwards et al., 2008; Xiang et al., 2010). Interestingly, lite-1 and Gr28b use a mix of secondary messengers and ion channels; for example, lite-1 interacts with Gi/o-proteins, guanylate cyclase, and cGMP to open CNG ion channels (Liu et al., 2010), while Gr28b uses TRPA1 ion channels (Xiang et al., 2010). As these unusual results clearly suggest, discovering previously unknown photoreceptor cells may reveal unique molecular solutions for detecting light.

Elucidating distinct phototransduction cascades contributes to a mechanistic understanding of variation in photoreceptor cell physiology and vice versa, as the state change of the ion channel following phototransduction changes the membrane potential of the cell. The direction of the voltage change depends on the type of phototransduction pathway involved. Using this link between biochemistry and physiology, we can generate testable hypotheses about which phototransduction cascade a cell utilizes through electrophysiological investigations of photocurrents using intracellular or patch-clamp recordings (e.g., Nasi & Gomez, 2009). For example, hyperpolarization (an increase in membrane potential) is seen in cells employing the Gt-opsin cascade, which involves CNG ion channels and phosphodiesterase (PDE). Depolarization (decrease in membrane potential) is seen in cells using the Gq-opsin cascade, and more specifically, the TRPC ion channel. However, membrane depolarization is also associated the Gs-opsin pathway, which uses CNG instead of TRPC, but differs from the Gt-opsin pathway by using AC instead of PDE. Using either PDE or AC alters whether the second messenger decreases (PDE) or increases (AC). How the second messenger acts on CNG ion channels depends on the direction of change in second messenger concentration and can cause hyperpolarization (for Gt-PDE cells) or depolarization (in Gs-AC cells) (see Su et al., 2006). Thus, while physiological data by itself can inform hypotheses about the underlying molecular machinery for phototransduction, integrating other types of data allows us to better understand photoreceptor cell functions and compare functions across cells types to address evolutionary questions.

Hypotheses and data for dispersed photoreception

Armed with our current understanding of the molecular basis of photoreception, we can incorporate molecular techniques, such as antibody staining and *in situ* hybridization, with existing data on behavior, morphology, and electrophysiology to locate and identify different photoreceptor cell types. By integrating data from different experimental approaches and taxa, we will gain a more comprehensive understanding of dispersed photoreception that we can use to form specific hypotheses about its mechanisms and evolution. Although there are data for dispersed photoreceptor cells from many

taxa, we have chosen to focus on four phyla that we believe currently provide the least incomplete data sets. In this section, we will present data from the literature that address three hypotheses regarding dispersed photoreceptor cells. Before embarking, however, it is worth defining spatial vision, a key idea for two of our hypotheses. An organ that provides spatial vision must be able to form at least a crude image and so must possess two or more photoreceptor cells (Land & Nilsson, 2002). This strict definition of spatial vision excludes cases where a single photoreceptor cell gathers directional information about light and allows an animal to move up or down a light gradient.

Behaviors mediated by dispersed photoreceptor cells

> Hypothesis I: Dispersed photoreceptor cells are used for many different tasks, but rarely any that require true spatial vision.

Mollusca

Behaviors mediated by dispersed photoreceptor cells are relatively well documented within the mollusks. These behaviors include phototaxis, which is the directional movement of an animal towards or away from light (Jekely, 2009), and the "shadow response," which describes an animal's defensive response to a sudden decrease in illumination. Neither of these tasks require an image-forming eye, only the ability to detect broad spatial or temporal differences in light intensity.

Eyeless bivalves display both phototaxis and a shadow response. *Lasaea rubra*, an eyeless lamellibranch, is negatively phototactic; photosensitivity is located at the animals' foot, not the relatively small and immobile siphon (Morton, 1960). However, in a number of other eyeless lamellibranchs, like *Mya* (Hecht, 1919; Light, 1930) and *Spisula* (Kennedy, 1960), siphon retraction in response to sudden increases or decreases in illumination is well documented. In these bivalves, the siphon tip is the most sensitive to light, although reduced responses can be elicited from other parts of the siphon (Light, 1930).

Gastropods also use dispersed photoreceptor cells for phototaxis and a shadow response. For example, the pond snail *Lymnaea stagnalis* orients positively to light and withdraws its head and foot under its shell when shaded (Willem, 1892; Liche, 1934, as cited in Duivenboden, 1982; Pieron, 1911; Dawson, 1911, as cited in Cook, 1975). These responses are observed even when an animal has been blinded or had its eyes and tentacles denervated (Cook, 1975, but see also Stoll, 1972, 1976; Duivenboden, 1982). *Nassarius reticulatus* also retracts its siphon and lowers its shell in response to shadows; again, both responses persist after eye removal (Crisp, 1972). Similarly, in *Onchidium verruculatum*, the shadow response persists following removal of stalk and dorsal eyes, but not after the removal of the labial palps and peripheral region of the mantle (Hisano et al., 1972b). Photosensitive central nervous system neurons in *Onchidium* do not respond to sudden changes in light and thus cannot contribute to the shadow response (Hisano et al., 1972b). Finally, siphons isolated from *Aplysia californica* habituate to both electrical stimuli as well as light, suggestive of dispersed photoreception (Lukowiak & Jacklet, 1972).

In polyplacophoran mollusks (or "chitons"), dispersed photoreceptor cells again appear to govern both phototaxis and a shadow response. In the eyeless *Chiton tuberculatus*, younger and older animals are negatively and positively phototactic, respectively; photosensitivity is likely conferred by dispersed receptor cells in the girdle and aesthetes, which are a set of projections from the peripheral nervous system that fill narrow channels in the dorsal shell plates (Arey & Crozier, 1919). Negative phototaxis has also been observed in a number of other eyeless chitons, including *Acanthochiton spiculosus* (Grancher, 1920), *Ischnochiton purpurascens* (Grancher, 1920), and *Ischnochiton maorianus* (Boyle, 1972). Nearly all chitons, including those without eyes, also display a defensive shadow response (Arey & Crozier, 1919; Boyle, 1972; Speiser et al., 2011), at times to very small changes in illumination, such as that caused by a fly passing overhead (Hyman, 1967).

Dispersed photoreception may also be present in cephalopods. Chromatophores, the pigmented neuromuscular organs responsible for dermal color patterning in these animals, may directly respond to light; however, descriptions of this phenomenon are minimal (Steinach, 1901 as cited in Steven, 1963). Chromatophores in denervated or low motor tone skin respond to brief flashes of light, after a 1 s delay, and in whole animals, populations of chromatophores in illuminated skin respond by expanding, whereas shaded skin pales (Packard & Brancato, 1993).

As demonstrated by the above examples, dispersed photoreception may be prevalent within mollusks. Furthermore, dispersed photoreceptor cells in this phyla mediate behaviors that are clearly important for an individual's survival, such as phototaxis and the shadow response Because these behaviors can be evoked in animals that naturally lack eyes, or even in experimentally blinded animals, it is evident that they do not rely on photoreceptor cells that confer spatial vision, a finding consistent with our hypothesis that dispersed photoreceptor cells generally mediate behaviors that do not require true spatial vision.

Cnidaria

Among the eyeless Cnidaria, behavioral responses to light vary (reviewed in Martin, 2002). In the anthozoan sea anemone *Metridium senile*, isolated mesenteries contract under light, even after anesthetization with magnesium chloride, which suggests that the parietal muscle may be directly photosensitive (Bohn, 1906 as cited in North, 1957; North & Pantin, 1958; Marks, 1976). Another sea anemone, *Calamactis praelongus*, has concentrations of nerves associated with regions of translucent skin in its oral disk and tentacles (Marks, 1976). Like *Metridium*, *Calamectis* also shows light sensitivity by some muscle cells, which leads to column bending. They can also detect light with sensory cells located near other muscles that are not themselves light sensitive (Marks, 1976). Yet another anemone, *Anthopleura elegantissima*, exhibits phototactic behavior correlated with the presence of symbiotic zooxanthellae (Pearse, 1974). This species (*A. elegantissima*) may also tune the photosynthetic behavior of its symbiotes in response to long-term changes in light conditions (Shick & Dykens, 1984). A related anthozoan, *Anthopleura xanthogrammica*, displays a range of wavelength-dependent behaviors: different wavelengths of UV and visible light are associated with specific behaviors such as tentacle flexion, tentacle retraction, and oral disk flexion (Clark & Kimeldorf, 1971).

So-called dispersed responses to light in animals without pigmentation or eyes are also known from polyps of each of the four Cnidarian classes (reviewed in Martin, 2002). For example, even though the hydrozoan *Hydra magnipapillata* lacks eyes or ocelli, dark-adapted animals display a series of predictable and repeatable postures that culminate in a tight retraction of the animal into its most condensed state upon presentation with bright light

(Passano & McCullough, 1962; Tardent & Frei, 1969). Overall, behaviors mediated by dispersed photoreceptor cells in Cnidaria are consistent with our behavioral hypothesis, as they mostly consist of phototactic movements and responses to changes in illumination. Furthermore, since many Cnidaria lack eyes entirely in one or more life stage, at least some of these behaviors cannot rely on photoreceptor cells that confer spatial vision.

Echinodermata

Light-influenced behaviors are well documented in echinoderms. These responses include phototaxis and a shadow response, as observed earlier in mollusks, as well as changes in pigmentation, podia extension and withdrawal, spine movement, covering, conspecific aggregation, and dark shelter seeking (see Millott, 1975). Many echinoderms have a classic shadow response, but brittle stars are also negatively phototactic and react strongly to direct illumination by moving towards darker areas (Cowles, 1910; Hendler, 1984). Several sea urchin species also use spatial information to detect and crawl towards (or away) from dark targets of certain sizes (Blevins & Johnsen, 2004; Yerramilli & Johnsen, 2010). Interestingly, the two urchin species in the above studies had different numbers and densities of spines, and the species with the more densely packed spines was able to detect smaller targets. Thus, spatial resolution in sea urchins may correlate with spine spacing, meaning that dispersed photoreceptor cells in urchins may act like the individual ommatidia of a compound eye spread across an entire animal's body (Woodley, 1982; Yerramilli & Johnsen, 2010). Brittle star chromatophores may serve a function similar to sea urchin spines, at least when it comes to light perception: the chromatophores are positioned at the skin surface and it is possible that they screen underlying photoreceptor cells in a manner that facilitates spatial vision (Aizenberg et al., 2001).

Unlike the other animals discussed thus far, sea urchins contradict our behavioral hypothesis by demonstrating that dispersed photoreceptor cells can provide spatial vision. Although further verification is necessary, brittle stars may provide a second counterexample to our hypothesis. Nevertheless, the most common light responses in echinoderms, phototaxis and shadow responses, do not necessarily require cells or organs specialized for spatial vision.

Arthropoda

Finally, although behaviors mediated by EOPCs have been reported in arthropods, behaviors specifically attributed to dispersed photoreception are rare. Some butterflies use a small set of EOPCs located at the end of their abdomens to control copulation in males and oviposition in females (Arikawa et al., 1997; Arikawa & Takagi, 2001). Recently, Xiang et al. (2010) determined that some light avoidance behaviors in *D. melanogaster* larvae are controlled by neurons that tile the body wall. In particular, these dispersed neurons mediate negative phototaxis in response to high-intensity short-wavelength light (blue-UV). Although data within Arthropoda are limited, the examples above demonstrate behaviors that are mediated by light intensity and wavelength, not spatial information, and are thus consistent with our behavioral hypothesis.

Morphology and neurophysiology of dispersed photoreceptor cells

Hypothesis II: Dispersed photoreceptor cells are rarely used for true spatial vision and so should not have the morphological features that allow other photoreceptor cells to maximize light gathering power or restrict the direction from which light is collected, such as expanded membrane surface areas or pigmentation, respectively.

Mollusca

Only a handful of dispersed photoreceptor cells have been identified in mollusks, so the morphology of these cells is not well established. Within bivalves, potential photoreceptor cells were identified by morphology in siphons from the clam *Mya*, but their presence has not been confirmed by other means (Light, 1930). These cells are similar in structure to phaosomes, photoreceptor cells best known from annelids that have a central intracellular cavity filled with large microvillous membranes (Röhlich et al., 1970). Pallial and peripheral siphonal neurons showed both excitatory and inhibitory response to light in the surf clam *Spisula* (Kennedy, 1960). However, the author could not determine if the recorded neurons were primary sensory cells responding directly to light or were higher-order cells responding to input from other photoreceptor cells.

Within the gastropods, sensory-type cells in *N. reticulatus* were identified in the siphon, but it is not clear if these cells function as photoreceptor cells (Crisp, 1972). Potential photoreceptor cells have also been identified in the tentacles, lips, and foot of *Lymnaea* (Zylstra, 1971). These cells possess a few (1–3) cilia, lie below the epidermal surface, and project dendrites to the surface between epidermal cells (Zylstra, 1971). The firing of inferior pedal nerves in *Lymnaea* are inhibited by light, although it is again not clear whether the recorded nerves are themselves primary sensors (Chono et al., 2002). Based on these limited data, the morphologies of putative photoreceptor cells in mollusks are consistent with our morphological hypothesis for dispersed photoreceptor cells. For example, the putative photoreceptor cells described above lack pigmentation and are not associated with pigment cells. Many of these cells do possess cilia or elaborated microvilli, however, which are morphological modifications associated with enhanced receptor sensitivity.

Cnidaria

Currently, there are no morphological studies of putative dispersed photoreceptor cells in Cnidaria, but neurophysiological experiments have confirmed and localized neural responses to light in this phylum. Marks (1976) recorded consistent pulses from the nerve net of *Calamectis* when light was directed at the upper portion of this anemone. He subsequently focused the light on 1-mm diameter spots, which occasionally evoked a similar neurophysiological pulse, although only when light was shone on the outer margin of the oral disc, and then only with longer exposure times than when the whole upper portion was illuminated. The specific sensory cells involved in this light response were not identified. An experiment on *A. elegantissima* (Sawyer et al., 1994) suggested that this animal's light response is conferred by endodermal cells, which runs counter to the observation that photoreceptor cells are generally confined to the ectoderm. Due to the sparseness of the data available in Cnidaria, it is difficult to draw any conclusions about dispersed photoreceptor cell morphology in these animals. Many cnidarians are unpigmented and lack the discrete pigment cells that are often associated with other types of photoreceptor cells. In this way at least, dispersed receptors in cnidarians are consistent with our morphological hypothesis.

Echinodermata

The morphological basis of dispersed photoreception in echinoderms is perhaps best understood in brittle stars (Ophiuroidea). The calcite skeleton of the brittle star *Ophiocoma wendtii* includes

plates that cover the arms and form a three-dimensional mesh with relatively regular small openings called stereom. Within the dorsal arm plates in *O. wendtii* and other photo-responsive brittle stars, some stereom contain transparent lens-shaped objects. It is hypothesized that these "microlenses" focus light onto bundles of neurons; it is also thought that they are actively shaded in bright environments by nearby chromatophores (Hendler & Byrne, 1987; Aizenberg et al., 2001). Extracellular recordings from the *O. wendtii* radial nerve cord confirm that photoreception occurs within this animal's arms (Cobb & Hendler, 1990). However, it is unknown whether the neurons that lie underneath the stereom are actually photosensitive. Ciliated cells at the tips of the arms of the brittle star *Ophiura ophiura* have also been identified as putative photoreceptor cells (Cobb & Moore, 1986). No recordings have been taken from these cells in either *O. ophiura* or *O. wendtii* due to the technical difficulty of accessing them under the skeleton (Cobb & Hendler, 1990). Like the brittle star stereom, sea urchin spines may allow dispersed photoreceptor cells to gather spatial information (Yerramilli & Johnsen, 2010). As in most echinoderms, relatively little is known about the location of sea urchin photoreceptor cells; however, recent evidence suggests that these cells may be found in sea urchin tube feet (Lesser et al., 2011).

Our morphological hypothesis predicts that dispersed photoreceptor cells will lack elaborated membranes and/or associations with pigmented cells because they are not used for spatial vision. As we have outlined earlier, behavioral studies indicate that dispersed photoreceptor cells in echinoderms may gather information that facilitates spatial vision. Although there have been no detailed morphological studies of dispersed photoreceptor cells in this phylum, these cells are often associated with pigmented cells. Thus, the morphology of dispersed photoreceptor cells in echinoderms is inconsistent with what we see in other phyla, but it is possible that echinoderms have evolved a unique method for gathering spatial information that relies on dispersed photoreceptors cells.

Arthropoda

There is limited evidence for dispersed photoreception among arthropods, but the examples we do know about provide us with our most detailed understanding of dispersed photoreceptor cell morphology. In the first example, dispersed photoreceptor cells in the butterfly *Papilio xuthus* have been described in microscopy studies. Here, there are four photoreceptor cells located near the *Papilio* genital region, two cells per side, associated with specific male or female anatomic structures (Arikawa et al., 1980). These cells are similar in structure to phaosomes, which are annelid photoreceptor cells with large intracellular microvillous membranes (Miyako et al., 1993; Arikawa & Miyako-Shimazaki, 1996). From extracellular recordings, we know that *Papilio*'s dispersed photoreceptor cells respond to flashes of light with a pattern of rapid firing, which decreases in frequency as light intensity decreases (Arikawa & Aoki, 1982). Ablation of these photoreceptor cells dramatically affects both male copulation and female oviposition behaviors (Arikawa et al., 1997; Arikawa & Takagi, 2001).

In a second example, green fluorescent protein expression in *D. melanogaster* larvae showed a set of photoreceptor cells (called class IV dendritic arborization neurons), which are tiled across the surface of their body wall; the dendritic arbors of these neurons fill much of the space between cell bodies (Grueber et al., 2002; Xiang et al., 2010). Short-wavelength light directed at these cells generated increased signals of the calcium indicator GCaMP3, which indicated that these cells directly respond to light. Genetic ablation of the class IV dendritic arborization neurons also decreased the light avoidance response of *Drosophila* larvae, while expression of channelrhodopsin-2 and stimulation with green light was sufficient to increase light avoidance in these animals, even when their larval eyes (Bolwig organs) were ablated (Xiang et al., 2010). Taken together, these results clearly indicate that the class IV dendritic arborization neurons are required for *D. melanogaster* larvae to avoid short wavelength light.

We hypothesize that dispersed photoreceptor cells lack the morphological modifications commonly seen in photoreceptor cells that provide spatial information. Consistent with our hypothesis, the dispersed photoreceptor cells in the two arthropods described above lack pigmentation. However, these cells do possess elaborated membranes. Expanded membrane surface area increases the number of visual pigment molecules potentially expressed by a cell, which in turn increases the proportion of available photons that a photoreceptor can gather. If a higher proportion of photons are collected by a photoreceptor, the photoreceptor is considered to have a higher sensitivity. It is evident then that dispersed photoreceptor cells in arthropods are modified so that their sensitivity is improved, but, because they lack any association with pigmented cells, it is unlikely that they gather spatial information. Thus, dispersed photoreceptor cell morphology in arthropods is consistent with our hypothesis that these cells are not used for spatial vision.

Molecular basis of dispersed photoreception

> Hypothesis III: Dispersed photoreception systems originated a number of times during evolution and may have co-opted existing phototransduction pathways.

Mollusca

With the exception of the pond snail *Lymnaea* and the cuttlefish *Sepia*, the phototransduction pathway genes involved in dispersed photoreception have not been identified in mollusks. In the gastropod *L. stagnalis*, the shadow responses of both sighted and blinded snails are not affected by a TRPC channel inhibitor, suggesting that the r-opsin (Gq-opsin) phototransduction pathway does not contribute to dispersed photoreception in this species (Pankey et al., 2010). However, the shadow response in this species is significantly hindered by exposure to the CNG channel inhibitor L-cis-diltiazem, which suggests that dispersed photoreception in *Lymnaea* is provided by CNG-dependent photoreceptor cells (Pankey et al., 2010). Based on consistent, observed associations between TRPC channels and light-induced cell membrane depolarization and between CNG channels and light-induced membrane hyperpolarization, these results indicate that a c-opsin (Gt- or Go-opsin) phototransduction cascade is used by *Lymnaea* dispersed photoreceptor cells. In contrast, the opsin messenger RNAs (mRNAs) expressed in the skin of the cuttlefish *Sepia officinalis* are similar to known cephalopod r-opsins (Mathger et al., 2010).

Previous investigations into the molecular basis of phototransduction in the retinal cells of *Lymnaea* (Chrachri & Nelson, 2005; Sakakibara et al., 2005) and *Sepia* (Brown & Brown, 1958; Bellingham et al., 1998) indicate pathways initiated by r-opsin (Gq-opsin). The observation that *Sepia* dispersed photoreceptor cells, like the retinal photoreceptor cells, rely on r-opsin suggests that retinal and dispersed photoreceptor cells in this animal share a common photoreceptor ancestor. In contrast, the use of CNG

ion channels, instead of TRP channels, by dispersed photoreceptor cells in *Lymnaea* suggests independent origins for dispersed and retinal photoreceptor cells in this snail. Finally, although there is insufficient information at this point about dispersed phototransduction cascades in other mollusks to generalize more broadly, *Lymnaea* and *Sepia* appear to use different phototransduction pathway genes for dispersed photoreception. This, combined with the differences between the phototransduction cascades employed by *Lymnaea* dispersed and retinal photoreceptor cells, suggests different evolutionary origins of dispersed photoreceptor cells in gastropods and cephalopods.

Cnidaria

The molecular components of dispersed photoreceptor cells have recently been determined in *H. magnipapillata* (Plachetzki et al., 2007; Plachetzki et al., 2010). These components in *Hydra* are similar to those involved with retinal cell phototransduction in the cubozoan (or "box jelly") eye (Koyanagi et al., 2008; Kozmik et al., 2008). The *Hydra* genome contains multiple opsin genes that, together with opsins from other cnidarians, form a distinct clade called cnidops (Plachetzki et al., 2007; but see Suga et al., 2008; Plachetzki et al., 2010). *In situ* hybridization indicates that these opsins are expressed in neurons throughout *Hydra* polyps, particularly those surrounding the hypostome (the apical region near the *Hydra* mouth). This pattern of opsin expression is consistent with the involvement of dispersed opsin-expressing photoreceptor cells in the light-induced contraction response observed in these animals. In addition, other phototransduction genes in *Hydra*, including CNG (Plachetzki et al., 2010), are co-expressed in the same cells as opsin. Behavioral assays further support a role for CNG in cnidarian phototransduction: the CNG channel inhibitor L-cis-diltiazem ablates the light-induced contraction response (Plachetzki et al., 2010). Finally, retinal photoreceptor cells in cubozoan eyes employ a previously unknown phototransduction pathway wherein cnidops initiates a Gs-AC cascade that leads to an increase of cAMP (Koyanagi et al., 2008). The full degree of similarity between this cubozoan phototransduction cascade and the cnidops-CNG pathway from *Hydra* dispersed photoreceptor cells remains unknown. If the cnidops-based cascade in cubozoans is also employed by *Hydra*, it will suggest that cubozoan retinal photoreceptor cells and hydrozoan dispersed photoreceptor cells may share an evolutionary history.

Echinodermata

The molecular components of phototransduction in echinoderms are known almost solely from genome sequence identity, rather than from functional studies. Six opsins were identified in an analysis of the sea urchin *Strongylocentrotus purpuratus* genome; all six of these opsins fall within the range of known metazoan opsins, but they are only distantly related to each other (Burke et al., 2006; Raible et al., 2006; Rubin et al., 2006). Furthermore, it was found that various opsins are expressed in the pedicellariae, tube feet, neural ring, and neural tube of adult animals (Raible et al., 2006). *In situ* expression patterns generated for several larval developmental stages and adult tube feet revealed that the urchin c-opsin homologue is expressed in widely dispersed cells (Ooka et al., 2010). Another study shows that urchin tube feet may express a second type of opsin as well (Lesser et al., 2011). Antibodies against bovine rhodopsin were also found to bind to optic cushions from sea star and brittle star arms (Johnsen, 1997). It is clear that several types of opsin are expressed in echinoderm dispersed photoreceptor cells, but, without functional data, it is difficult to properly categorize these photoreceptors or associate particular behaviors with their presence. Thus, it is difficult to evaluate how many times dispersed photoreceptor cells have evolved in echinoderms or whether these cells are closely related to any other described photoreceptors in Metazoa.

Arthropoda

The only well-described phototransduction pathway for dispersed photoreception in arthropods is that found in *D. melanogaster* larvae. Light avoidance behaviors were maintained in *D. melanogaster* larvae that were mutants in rhodopsins and cryptochrome, suggesting that neither molecule was used by class IV dendritic arborization neurons to mediate light avoidance. Instead, the authors found that *Gr28b*, a *Drosophila* homologue of the *C. elegans* photopigment *lite-1*, was required for light responses using P-elements insertions and RNA interference (RNAi), although it is not yet not clear from these experiments whether *Gr28b* directly senses light (Xiang et al., 2010). Furthermore, dispersed photoreceptor cells in *D. melanogaster* larvae likely employ the thermosensor TrpA1, a homologue of the mammalian TrpA, for responding to light, as *TrpA1* RNAi expression in class IV dendritic arborization neurons abolished light-induced changes in firing rates in these cells (Xiang et al., 2010). These phototransduction cascade genes, particularly *Gr28b*, do not fit into any canonical opsin-based pathway and represent unique molecular solutions to light detection in this species. It is not yet clear whether this new type of phototransduction cascade is used by any closely related insect species or whether it is widespread throughout the arthropods. Given its novelty, however, this cascade clearly represents an independent evolution of the phototransduction pathway for dispersed photoreceptor cells. We hypothesized that dispersed phototransduction cascades evolved from existing molecular components involved with phototransduction. The novel cascades found in *Drosophila* larvae contradict this hypothesis, as *Gr28b* is most closely related to gustatory receptors and *TrpA1* is a member of an ion channel family typically associated with temperature detection.

Discussion

Dispersed photoreception, or the "dermal light sense", has long presented a number of mechanistic and evolutionary conundrums for biologists. Some mechanistic questions include: What cells underlie dispersed photoreception? How is dispersed photoreception used by animals? Do the same physiological and molecular mechanisms underlie dispersed photoreception in all animals? We are also interested in evolutionary questions, such as how did dispersed photoreceptor cells originate in different groups and how are these receptors related to other photoreceptor cells? Our goal for this paper was to better understand the dermal light sense in the context of the integrative biology of photoreceptor cells. Specifically, we had three main goals for this review: a) to present a new objective classification scheme for photoreceptor cells that will help facilitate comparisons between different photoreceptor cell types, b) to provide key observations concerning what is known about distributed photoreceptor cells in different animals and to propose three hypotheses regarding dispersed photoreception, and 3) to discuss how the study of dispersed photoreceptor cells informs our general understanding of metazoan photoreceptor origin, evolution, function, and diversity.

Classification of photoreceptor cell types

Our proposed classification scheme allows us to place any photoreceptor cell within one of four quadrants. These quadrants are defined by two axes: the first indicates the spatial relationship between a given photoreceptor and the other photoreceptor cells in an animal, while the second describes the way a photoreceptor interacts with the rest of an animal's nervous system (see Fig. 1). Our classification scheme allows us to make a number of comparisons between photoreceptor cells that share a quadrant, much as we have done for some photoreceptor cells that are dispersed first-order neurons. It also lets us explore hypotheses about the function and evolution of cells in a quadrant. For instance, the majority of photoreceptor cells used for spatial vision are aggregated first-order neurons that fall within Quadrant III. This grouping prompts a number of questions that we can now ask about these cells: Are there requirements for spatial vision that almost always necessitate that photoreceptor cells be aggregated? If there are, how do echinoderms like sea urchins, which seem to have spatial vision despite only having dispersed photoreceptor cells, overcome these requirements? Could their spherical body shape contribute? Similarly, we also classified photoreceptor cells by their neural network position as either sensory cells (first order) or other neural functions (higher order). Do first-order and higher-order cells mediate similar types of light-influenced behavior? Are certain types of cell better suited for particular tasks than others? Finally, we wonder why we have no good examples of dispersed higher-order photoreceptor cells. This might be due to discovery bias, as dispersed photoreceptor cells generally lack pigment and relatively few higher-order neurons have been investigated for light sensitivity.

Three hypotheses for dispersed photoreceptor cells

Dispersed photoreceptor cells are used for behaviors that do not require true spatial vision

Animals can use non-directional light information to set circadian cycles, gauge depth, monitor UV levels, detect a predator's shadow, or, in burrowing animals, find a substrate surface (reviewed by Nilsson, 2009). Additionally, behaviors like phototaxis require directional, but not necessarily spatial, information about light. In many cases, the photoreceptor cells mediating these tasks lie outside the eyes in so-called extraocular photoreceptor cells or EOPCs. Our classification scheme splits EOPCs into at least two groups: those that are aggregated high-order neurons (Quadrant I) and those that are dispersed first-order neurons (Quadrant IV). Given what we know about these two types of photoreceptor, it appears that aggregated high-order neurons, like those found within ganglia in *Onchidium* or ipRGCs in mammalian eyes, are employed for a different set of non-visual tasks than dispersed first-order photoreceptor cells. For example, light-sensitive interneurons in the abdominal ganglia of *Onchidium* are thought to influence tactile and water pressure inputs associated with mantle-levitating or pneumostome-closing behaviors (reviewed in Gotow & Nishi, 2008). Melanopsin (r-opsin) expressing ipRGCs are important for circadian responses, such as pupil reflexes and photoentrainment, in mammals (Panda et al., 2002; Hattar et al., 2003). Thus, aggregated higher-order photoreceptor cells may preferentially be used for tasks associated with relatively long-term physiological responses like photoentrainment. In contrast, we have presented evidence that suggests that dispersed first-order photoreceptor cells are used for short-term movement-based behavioral responses such as phototaxis and shadow responses. Furthermore, based on these behaviors, dispersed photoreceptor cells are capable of collecting both directional and non-directional light information. While we have a lot to learn about these two very different classes of photoreceptor cells, it appears that each may be specialized for particular tasks related to either directional or non-directional light collection, but most often not true spatial vision.

Dispersed photoreceptor cells are morphologically unspecialized

Our hypothesis for the general lack of morphological specialization in dispersed photoreceptor cells is that they are rarely used to gather spatial information and, thus, need neither pigmentation nor a close association with pigmented cells. Our hypothesis also implies that dispersed photoreceptor cells may not require the increased sensitivity afforded by elaborated membranes (reviewed by Nilsson, 2009). To the extent that dispersed photoreceptor cells have been positively confirmed in the four focal phyla, support for this hypothesis is ambiguous. Putative dispersed photoreceptor cells in bivalves and gastropods are not pigmented. Some appear to possess cilia, but the cilia themselves are not folded. However, those cells that resemble phaosomes, like those described in the clam *Mya*, do have expanded microvilli. In the cnidarian *Hydra*, photoreceptor cells located near the group of battery cells associated with nematocysts lack both pigmentation and membrane folding. However, the morphologies of dispersed cells in echinoderms and arthropods do possess some specializations for directional light collection. In the echinoderms, putative photoreceptor cells beneath the brittle star stereom were identified; these cells possessed fine neural processes but lacked membrane elaboration or pigmentation. However, separate pigment cells in echinoderms, specifically chromatophores in brittle stars and spines in sea urchins, are thought to interact with these neurons in response to light. Finally, in the arthropods, both examples we present show evidence of membrane expansion but not pigmentation. The cells in butterfly genitalia resemble phaosomes, which possess an extracellular space that is filled with microvilli. In *Drosophila* larvae, the ligh-sensitive neurons bear large dendritic arborizations, which increase the surface area of each cell.

How are these photoreceptor cells used by animals in these four phyla? Shadow-response-like movement and contraction are particularly common in the mollusks and echinoderms, and hydra also retract into compact balls when illuminated. These types of behaviors do not necessarily require directional information about light. Conversely, some animals, such as many mollusks, appear to use dispersed photoreceptor cells for directional tasks like phototaxis. Other animals, such as sea urchins (and potentially brittle stars), are able to use dispersed photoreceptor cells for spatial vision. Thus, we can state that a close association between photoreceptor cells and pigment cells is normally required for spatial vision, but in some cases, the opaque body of an animal (or large portions of an animal) can provide the screening necessary for spatial information to be gathered (Milne & Milne, 1956, as cited in Yoshida, 1979). In these cases, then, we might expect to see some membrane elaboration, which allows increased light collection, to compensate for photons lost through screening.

An alternative hypothesis for why some dispersed photoreceptor cells lack morphological specializations is that these cells may be constrained, morphologically, by factors not directly related to photodetection, namely the maintenance of multifunctionality. Empirical evidence for this hypothesis is scarce. However, multifunctionality can arise from dispersed receptors being either multimodal sensors or higher-order neurons that receive input from both other neurons and the external environment. For

example, cells associated with nematocysts in *Hydra* express mRNAs that code for opsin and CNG (Plachetzki et al., 2010). From previous studies, we know that nematocyst firing is influenced by both mechano- and chemosensory stimuli (Watson & Hessinger, 1989, 1994), and it appears likely that these opsin-expressing cells in *Hydra* may also contribute to the nematocyst firing response. Finally, although they do not fall under the definition of dispersed photoreceptor cells, multimodal sensory neurons have been identified in *C. elegans*. These ciliated cells respond to both light and electrical stimulation (Gabel et al., 2007; Ward et al., 2008).

Some dispersed photoreceptor cells may also be higher-order neurons (in that they receive input from other cells). Although they are not dispersed photoreceptor cells, retinal ganglion cells (RGCs) in the vertebrate eye are known to be photosensitive third-order neurons; functionally similar interneurons could very well be common. The abdominal ganglion photoreceptor cells found in the marine gastropod *Onchidium* are another well-documented example of photosensitive higher-order neurons. These cells function as both interneurons and photoreceptors but maintain a fairly typical neural morphology that allows them to interact with many other neurons via synapses (reviewed in Gotow & Nishi, 2008). Multifunctionality could thus constrain the morphology of these higher-order photoreceptor cells by not allowing them to evolve the elaborated membranes that help bolster the sensitivity of retinal photoreceptor cells.

Dispersed photoreceptor cells use a variety of phototransduction pathways

We have noted that dispersed photoreceptor cells use a variety of phototransduction pathways. Thus, we conclude that dispersed EOPCs have evolved a number of times within the Metazoa, possibly by co-opting existing phototransduction cascades. This conclusion appears to hold for our four focal phyla. We have evidence that dispersed photoreceptor cells may have evolved more than once within the mollusks, as the cuttlefish *Sepia* uses r-opsin for both retinal and dispersed photoreceptor cells, whereas dispersed phototransduction in the pond snail *Lymnaea* relies on CNG and, potentially, c-opsin. The cnidarians appear to use a unique form of the opsin protein, cnidops, as well as CNG for their ion channels. Echinoderms have at least six different opsins, and we do not yet have a clear consensus about the specific type of phototransduction cascade employed by echinoderm dispersed photoreceptor cells, which makes it difficult to conjecture about the evolutionary origins of these cells. Finally, the presence of non-opsin based light sensitivity in cells tiling *Drosophila* larvae clearly indicate a system evolutionarily unrelated to opsin-based systems. Overall, molecular evidence relating to phototransduction cascades suggests that at least some dispersed photoreceptor cells have evolved independently in mollusks, cnidarians, and arthropods and that these cells may have even evolved more than once with each phylum.

Dispersed photoreceptor cells in the context of photoreceptor cell evolution

Given that dispersed photoreceptor cells have likely evolved multiple times during Metazoan history, how did these cells originate? Also, what is the evolutionary relationship between dispersed photoreceptor cells and other receptors, including other photoreceptor cells within the same animal? Here our classification scheme provides characters that, combined with a greater understanding of the phototransduction cascades employed by different photoreceptor cells, may help unravel the relationship between different photoreceptor cell types. For instance, we suggest that when different dispersed photoreceptor cells use different phototransduction cascade genes, they likely evolved separately. We can apply this same logic to photoreceptor cells types within an individual animal: differences in phototransduction cascades within the same animal suggest possible independent evolution of photoreceptor cell types. This may be the case in the pond snail *Lymnaea*, as this snail's dispersed photoreceptor cells seem to use CNG, while their retinal photoreceptor cells depolarize with light stimulation, implicating TRP (or possibly CNG coupled with AC) as the ion channel responsible for retinal phototransduction.

The scenario described above may not be unusual in animals; for instance, the melanopsin expressing intrinsically light-sensitive RGCs in vertebrate eyes have only been identified relatively recently. Thus, vertebrate eyes possess two types of photoreceptor cells that likely use distinct phototransduction pathway genes: the canonical c-opsin pathway found in rods and cones, as well as a pathway initiated by melanopsin, which is closely related to the r-opsin found in invertebrate eyes (Hattar, 2002; Tarttelin et al., 2003). These two photoreceptor types also fall into different quadrants within our classification scheme, rods and cones into the aggregated/first-order quadrant, and RGCs into the aggregated/higher-order quadrant. Given the morphological and molecular differences between these two types of vertebrate photoreceptor cells, we could propose hypotheses to account for the differences we see. For instance, we could ask whether RCGs, which are relatively morphologically unspecialized, are constrained by their function as interneurons or whether they are sufficiently sensitive to light without extensive membrane elaboration.

Finally, we may be able to ask broader evolutionary questions regarding photoreception systems. For instance, what the ancestral Metazoan photoreceptor may have looked like, how phototransduction cascade genes evolved and diversified and what the evolutionary relationship may be between phototransduction and other signal transduction pathways and other sensory modalities. By understanding different types of photoreceptor cells and photoreception systems, we may be able to better understand the evolution of eyes, a question that has challenged many evolutionary biologists, including Darwin.

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After this review was accepted for publication, Ullrich-Luter et al. (2011) reported that Sp-op4 (a r-opsin) and Sp-pax6 are expressed by photoreceptor cells in the tube feet of adult sea urchins. These cells possess surface areas expanded via microvilli, but lack any pigmentation; they also appear to confer true spatial vision to sea urchins. The morphology of these photoreceptors, alongside r-opsin expression, suggests that they are rhabdomeric type cells. Overall, these new results are consistent with two of our hypotheses for dispersed photoreceptor cells, as they show that sea urchin photoreceptors are first order cells that lack pigmentation and use r-opsin for true spatial vision (no other deuterostome is known to use an r-opsin for this purpose). Finally, this paper highlights how uncovering the mechanisms that underlie dispersed photoreceptor cells is important to understanding the evolution of photosensory systems generally.

References

Adler, K. (1976). Extraocular photoreception in amphibians. *Photochemistry and Photobiology* **23**, 275–298.

Aizenberg, J., Tkachenko, A., Weiner, S., Addadi, L. & Hendler, G. (2001). Calcitic microlenses as part of the photoreceptor system in brittlestars. *Nature* **412**, 819–822.

Arendt, D. (2003). Evolution of eyes and photoreceptor cell types. *International Journal of Developmental Biology* **47**, 563–572.

Arendt, D., Tessmar-Raible, K., Snyman, H., Dorresteijn, A.W. & Wittbrodt, J. (2004). Ciliary photoreceptors with a vertebrate-type opsin in an invertebrate brain. *Science* **306**, 869–871.

Arendt, D. & Wittbrodt, J. (2001). Reconstructing the eyes of Urbilateria. *Philosophical Transactions of the Royal Society B: Biological Sciences* **356**, 1545–1563.

Arey, L. & Crozier, W. (1919). The sensory responses of *Chiton*. *Journal of Experimental Zoology* **29**, 157–260.

Arikawa, K. & Aoki, K. (1982). Response characteristics and occurrence of extraocular photoreceptors on lepidopteran genitalia. *Journal of Comparative Physiology A: Neuroethology, Sensory, Neural, and Behavioral Physiology* **148**, 483–489.

Arikawa, K., Eguchi, E., Yoshida, A. & Aoki, K. (1980). Multiple extraocular photoreceptive areas on genitalia of butterfly *Papilio xuthus*. *Nature* **288**, 700–702.

Arikawa, K. & Miyako-Shimazaki, Y. (1996). Combination of physiological and anatomical methods for studying extraocular photoreceptors on the genitalia of the butterfly, *Papilio xuthus*. *Journal of Neuroscience Methods* **69**, 75–82.

Arikawa, K., Suyama, D. & Fujii, T. (1997). Hindsight by genitalia: Photo-guided copulation in butterflies. *Journal of Comparative Physiology A: Neuroethology, Sensory, Neural, and Behavioral Physiology* **180**, 295–299.

Arikawa, K. & Takagi, N. (2001). Genital photoreceptors have crucial role in oviposition in Japanese yellow swallowtail butterfly, *Papilio xuthus*. *Zoological Science* **18**, 175–179.

Arvanitaki, A. & Chalazonitis, N. (1961). Excitatory and inhibitory processes initiated by light and infra-red radiations in single identifiable nerve cells. In *Nervous Inhibition*, ed. Florey, E. New York: Pergamon Press, 194–231.

Bagnara, J. & Obika, M. (1967). Light sensitivity of melanophores in neural crest explants. *Experimentia* **23**, 155–157.

Barber, V. & Wright, D. (1969). The fine structure of the eye and optic tentacle of the mollusc *Cardium edule*. *Journal of Ultrastructure Research* **26**, 515–528.

Bellingham, J., Morris, A. & Hunt, D. (1998). The rhodopsin gene of the cuttlefish *Sepia officinalis*: Sequence and spectral tuning. *The Journal of Experimental Biology* **201**, 2299–2306.

Blevins, E. & Johnsen, S. (2004). Spatial vision in the echinoid genus *Echinometra*. *Journal of Experimental Biology* **207**, 4249–4253.

Bolwig, N. (1946). Senses and sense organs of the anterior end of the house fly larvae. *Dansk Naturhist for Kobenhavn Vidensk Meddel* **109**, 81–217.

Boyle, P. (1969). Rhabdomeric ocellus in a chiton. *Nature* **222**, 895–896.

Boyle, P. (1972). The aesthetes of chitons. *Marine and Freshwater Behaviour and Physiology* **1**, 171–184.

Brown, P. & Brown, P. (1958). Visual pigments of the octopus and cuttlefish. *Nature* **182**, 1288–1290.

Burke, R., Angerer, L., Elphick, M., Humphrey, G., Yaguchi, S., Kiyama, T., Liang, S., Mu, X., Agca, C. & Klein, W. (2006). A genomic view of the sea urchin nervous system. *Developmental Biology* **300**, 434–460.

Cashmore, A.R., Jarillo, J.A., Wu, Y. & Liu, D. (1999). Cryptochromes: Blue light receptors for plants and animals. *Science* **284**, 760–765.

Chono, K., Fujito, Y. & Ito, E. (2002). Non-ocular dermal photoreception in the pond snail *Lymnaea stagnalis*. *Brain Research* **951**, 107–112.

Chrachri, A. & Nelson, L. (2005). Whole-cell recording of light-evoked photoreceptor responses in a slice preparation of the cuttlefish retina. *Visual Neuroscience* **22**, 359–370.

Clark, E.D. & Kimeldorf, D.J. (1971). Behavioral reactions of the sea anemone, *Anthopleura xanthogrammica*, to ultraviolet and visible radiations. *Radiation Research* **45**, 166–175.

Cobb, J. & Hendler, G. (1990). Neurophysiological characterization of the photoreceptor system in a brittlestar, *Ophiocoma wendtii* (Echinodermata, Ophiuroidea). *Comparative Biochemistry and Physiology A: Physiology* **97**, 329–333.

Cobb, J. & Moore, A. (1986). Comparative studies on receptor structure in the brittlestar *Ophiura ophiura*. *Journal of Neurocytology* **15**, 97–108.

Cobb, C. & Williamson, R. (1998*a*). Electrophysiology and innervation of the photosensitive epistellar body in the lesser octopus *Eledone cirrhosa*. *The Biological Bulletin* **195**, 78–87.

Cobb, C. & Williamson, R. (1998*b*). Electrophysiology of extraocular photoreceptors in the squid *Loligo forbesi* (Cephalopoda: Loliginidae). *Journal of Molluscan Studies* **64**, 111–117.

Cobb, C.S., Williamson, R. & Pope, S.K. (1995). The responses of the epistellar photoreceptors to light and their effect on circadian rhythms in the lesser octopus, *Eledone cirrhosa*. *Marine and Freshwater Behaviour and Physiology* **26**, 59–69.

Cook, A. (1975). The withdrawal response of a freshwater snail (*Lymnaea stagnalis* L.). *Journal of Experimental Biology* **62**, 783–796.

Cowles, R. (1910). Stimuli produced by light and by contact with solid walls as factors in the behavior of ophiuroids. *Journal of Experimental Biology* **9**, 387–416.

Crisp, M. (1972). Photoreceptive function of an epithelial receptor in *Nassarius reticulatus* [Gastropoda, Prosobranchia]. *Journal of the Marine Biological Association of the United Kingdom* **52**, 437–442.

Diggle, P. (2003). *Statistical Analysis of Spatial Point Patterns*. Arnold, London.

Dilly, P. & Wolken, J. (1973). Studies on the receptors in *Ciona intestinalis*. IV. The ocellus in the adult. *Micron* **4**, 11–29.

Dörjes, J. (1968). Die Acoela (Turbellaria) der deutschen Nordseeküste und ein neues System der Ordnung. *Zeitschrift fuer Zoologische Systematik und Evolutionsforschung* **6**, 56–452.

Duivenboden, Y. (1982). Non-ocular photoreceptors and photo-orientation in the pond snail *Lymnaea stagnalis* (L.). *Journal of Comparative Physiology A: Neuroethology, Sensory, Neural, and Behavioral Physiology* **149**, 363–368.

Eakin, R. (1961). Photoreceptors in the amphibian frontal organ. *Proceedings of the National Academy of Sciences* **47**, 1084–1088.

Eakin, R. (1968). Evolution of photoreceptors. In *Evolutionary Biology*, **Vol 2**, eds. Dobzhansky, T., Hecht, M., and Steere, W., pp. 194–242. Appleton-Century-Crofts: New York.

Eakin, R. (1972). Structure in invertebrate photoreceptors. In *Handbook of Sensory Physiology*, **Vol. 7**, ed. Dartnell, H.J., pp. 635–684. New York: Springer New York.

Eakin, R. & Brandenburger, J. (1967). Differentiation in eye of a pulmonate snail *Helix aspersa*. *Journal of Ultrastructure Research* **18**, 391–421.

Eakin, R. & Westfall, J.A. (1962). Fine structure of photoreceptors in *Amphioxus*. *Journal of Ultrastructure Research* **6**, 531–539.

Edwards, S., Charlie, N., Milfort, M., Brown, B., Gravlin, C., Knecht, J. & Miller, K. (2008). A novel molecular solution for ultraviolet light detection in *Caenorhabditis elegans*. *PLoS Biology* **6**, 1715–1729.

Fu, Y. & Yau, K.W. (2007). Phototransduction in mouse rods and cones. *Pflügers Archiv: European Journal of Physiology* **454**, 805–819.

Gabel, C.V., Gabel, H., Pavlichin, D., Kao, A., Clark, D.A. & Samuel, A.D.T. (2007). Neural circuits mediate electrosensory behavior in *Caenorhabditis elegans*. *Journal of Neuroscience* **27**, 7586–7596.

Gomez, M.P. & Nasi, E. (2000). Light Transduction in Invertebrate Hyperpolarizing Photoreceptors: Possible Involvement of a Go-Regulated Guanylate Cyclase. *Journal of Neuroscience* **20**, 5254–5263.

Gotow, T. (1975). Morphology and function of the photoexcitable neurones in the central ganglia of *Onchidium verruculatum*. *Journal of Comparative Physiology A: Neuroethology* **99**, 139–152.

Gotow, T. & Nishi, T. (2002). Light-dependent K channels in the mollusc Onchidium simple photoreceptors are opened by cGMP. *Journal of General Physiology* **120** (4): 581–597. doi:10.1085/jgp.20028619.

Gotow, T. & Nishi, T. (2008). Simple photoreceptors in some invertebrates: Physiological properties of a new photosensory modality. *Brain Research* **1225**, 3–16.

Grancher, J. (1920). Note on the photic sensitivity of the chitons. *The American Naturalist* **54**, 376–380.

Grueber, W., Jan, L. & Jan, Y. (2002). Tiling of the *Drosophila* epidermis by multidendritic sensory neurons. *Development* **129**, 2867–2878.

Hara, T. & Hara, R. (1980). Retinochrome and rhodopsin in the extraocular photoreceptor of the squid, *Todarodes*. *The Journal of General Physiology* **75**, 1.

Hardie, R. & Raghu, P. (2001). Visual Transduction in Drosophila. *Nature.* **413**, 186–193.

Hattar, S., Lucas, R.J., Mrosovsky, N., Thompson, S., Douglas, R., Hankins, M.W., Lem, J., Biel, M., Hofmann, F. & Foster, R.G. (2003). Melanopsin and rod-cone photoreceptive systems account for all major accessory visual functions in mice. *Nature* **424**, 75–81.

Haug, G. (1933). Die Lichtreaktionen der Hydren (Chlorohydra viridissima und Pelmatohydra oligactis). *Zeitschrift für Vergleichende Physiologie* **19**, 354–355.

Heath, H. (1904). The larval eye of chitons. *Proceedings of the Academy of Natural Sciences of Philadelphia* **56**, 257–259.
Hecht, S. (1919). Sensory equilibrium and dark adaptation in *Mya arenaria*. *The Journal of General Physiology* **1**, 545–558.
Hegemann, P. (2008). Algal sensory photoreceptors. *Annual Review of Plant Biology* **59**, 167–189.
Hendler, G. (1984). Brittlestar color-change and phototaxis (Echinodermata: Ophiuroidea: Ophiocomidae). *Marine Ecology* **5**, 379–401.
Hendler, G. & Byrne, M. (1987). Fine structure of the dorsal arm plate of *Ophiocoma wendtii*: Evidence for a photoreceptor system (Echinodermata, Ophiuroidea). *Zoomorphology* **107**, 261–272.
Hisano, N., Tateda, H. & Kuwabara, M. (1972*a*). An electrophysiological study of the photo-excitative neurones of *Onchidium verruculatum* in situ. *Journal of Experimental Biology* **57**, 661–671.
Hisano, N., Tateda, H. & Kuwabara, M. (1972*b*). Photosensitive neurones in the marine pulmonate mollusc *Onchidium verruculatum*. *Journal of Experimental Biology* **57**, 651.
Howard, L. (2008). Drosophilidae compound eye edit. Photo. http://commons.wikimedia.org/wiki/File:Drosophilidae_compound_eye_edit1.jpg.
Hyman, L. (1951). *The Invertebrates: Acanthocephala, Aschelminthes, and Entoprocta, the Pseudocoelomate Bilateria*, **Vol. 3**. McGraw-Hill, New York: London.
Hyman, L. (1967). *The Invertebrates. Vol. VI. Mollusca I. Aplacophora, Polyplacophora, Monoplacophora, Gastropoda. The Coelomate Bilateria*. McGraw-Hill, New York: London.
Jekely, G. (2009). Evolution of phototaxis. *Philosophical Transactions of the Royal Society B: Biological Sciences* **364**, 2795–2808.
Johnsen, S. (1997). Identification and localization of a possible rhodopsin in the echinoderms *Asterias forbesi* (Asteroidea) and *Ophioderma brevispinum* (Ophiuroidea). *The Biological Bulletin* **193**, 97–105.
Kennedy, D. (1960). Neural photoreception in a lamellibranch mollusc. *Journal of General Physiology* **44**, 277–299.
Kennedy, D. (1963). Physiology of photoreceptor neurons in the abdominal nerve cord of the crayfish. *The Journal of General Physiology* **46**, 551.
Kojima, D., Terakita, A. & Ishikawa, T. (1997). A novel Go-mediated phototransduction cascade in scallop visual cells. *Journal of Biological Chemistry* **272**, 22979–22982.
Koyanagi, M., Kubokawa, K. & Tsukamoto, H. (2005). Cephalochordate melanopsin: Evolutionary linkage between invertebrate visual cells and vertebrate photosensitive retinal ganglion cells. *Current Biology* **15**, 1065–1069.
Koyanagi, M., Takano, K., Tsukamoto, H. & Ohtsu, K. (2008). Jellyfish vision starts with cAMP signaling mediated by opsin-Gs cascade. *Proceedings of the National Academy of Sciences* **105**, 15576–15580.
Koyanagi, M., Terakita, A., Kubokawa, K. & Shichida, Y. (2002). Amphioxus homologs of Go-coupled rhodopsin and peropsin having 11-cis-and all-trans-retinals as their chromophores. *FEBS Letters* **531**, 525–528.
Kozmik, Z., Ruzickova, J. & Jonasova, K. (2008). Assembly of the cnidarian camera-type eye from vertebrate-like components. *Proceedings of the National Academy of Sciences* **105**, 8989–8993.
Kusakabe, T., Kusakabe, R., Kawakami, I., Satou, Y., Satoh, N. & Tsuda, M. (2001). Ci-opsin1, a vertebrate-type opsin gene, expressed in the larval ocellus of the ascidian *Ciona intestinalis*. *FEBS Letters* **506**, 69–72.
Kusakabe, T. & Tsuda, M. (2007). Photoreceptive systems in ascidians. *Photochemistry and Photobiology* **83**, 248–252.
Lacalli, T. (2004). Sensory systems in amphioxus: A window on the ancestral chordate condition. *Brain Behavior and Evolution* **64**, 148–162.
Land, M.F. & Nilsson, D.-E. (2002). *Animal Eyes*. Oxford University Press Oxford; Toronto.
Lesser, M.P., Carleton, K.L., Bottger, S.A., Barry, T.M. & Walker, C.W. (2011). Sea urchin tube feet are photosensory organs that express a rhabdomeric-like opsin and PAX6. *Proceedings of the Royal Society B: Biological Sciences*. doi:10.1098/rspb.2011.0336.
Light, V. (1930). Photoreceptors in *Mya arenaria*, with special reference to their distribution, structure, and function. *Journal of Morphology* **49**, 1–43.
Liu, J., Ward, A., Gao, J., Dong, Y., Nishio, N., Inada, H., Kang, L., Yu, Y., Ma, D., Xu, T., Mori, I., Xie, Z. & Xu, X.Z. (2010). *C. elegans* phototransduction requires a G protein-dependent cGMP pathway and a taste receptor homolog. *Nature Neuroscience* **13**, 715–722.
Lukowiak, K. & Jacklet, J. (1972). Habituation and dishabituation: Interactions between peripheral and central nervous systems in *Aplysia*. *Science* **178**, 1306–1308.
Mano, H. & Fukada, Y. (2007). A median third eye: Pineal gland retraces evolution of vertebrate photoreceptive organs. *Photochemistry and Photobiology* **83**, 11–18.
Marks, P. (1976). Nervous control of light responses in the sea anemone, *Calamactis praelongus*. *Journal of Experimental Biology* **65**, 85–96.
Martin, V. (2002). Photoreceptors of cnidarians. *Canadian Journal of Zoology* **80**, 1703–1722.
Mathger, L.M., Roberts, S.B. & Hanlon, R.T. (2010). Evidence for distributed light sensing in the skin of cuttlefish, *Sepia officinalis*. *Biology Letters* **6**, 600–603.
Mauro, A. (1977). Extra-ocular photoreceptors in cephalopods. *Symposium of the Zoological Society of London* **38**, 287–308.
Millott, N. (1968). The dermal light sense. *Symposia of the Zoological Society of London* **23**, 1–36.
Millott, N. (1975). The photosensitivity of echinoids. *Advances in Marine Biology* **13**, 1–52.
Milne, L. & Milne, M. (1956). Invertebrate photoreceptors. In *Radiation Biology*, **Vol. 3**. ed. Hollaender, A. McGraw-Hill New York 621–692.
Miyako, Y., Arikawa, K. & Eguchi, E. (1993). Ultrastructure of the extraocular photoreceptor in the genitalia of a butterfly, *Papilio xuthus*. *The Journal of Comparative Neurology* **327**, 458–468.
Morton, J. (1960). The responses and orientation of the bivalve *Lasaea rubra* Montagu. *Journal of the Marine Biological Association of the United Kingdom* **39**, 5–26.
Mrabet, Y. (2008). Drosophila XY sex-chromosomes. Drawing. http://commons.wikimedia.org/wiki/File:Drosophila_XY_sex-determination.svg.
Nasi, E. & Del Pilar Gomez, M. (2009). Melanopsin-mediated light-sensing in amphioxus: A glimpse of the microvillar photoreceptor lineage within the deuterostomia. *Communicative and Integrative Biology* **2**, 441–443.
Nilsson, D. (1994). Eyes as optical alarm systems in fan worms and ark clams. *Philosophical Transactions: Biological Sciences* **346**, 195–212.
Nilsson, D. (2009). The evolution of eyes and visually guided behaviour. *Philosophical Transactions of the Royal Society B: Biological Sciences* **364**, 2833–2847.
Nishioka, R., Hagadorn, I. & Bern, H. (1962). Ultrastructure of the epistellar body of the octopus. *Cell and Tissue Research* **57**, 406–421.
Nishioka, R., Yasumasu, I., Packard, A., Bern, H. & Young, J. (1966). Nature of vesicles associated with the nervous system of cephalopods. *Cell and Tissue Research* **75**, 301–316.
Nordstrom, K., Wallen, R., Seymour, J. & Nilsson, D. (2003). A simple visual system without neurons in jellyfish larvae. *Proceedings of the Royal Society B: Biological Sciences* **270**, 2349–2354.
North, W.J. (1957). Sensitivity to light in the sea anemone *Metridium senile* (L.). *The Journal of General Physiology* **40**, 715–733.
North, W. & Pantin, C. (1958). Sensitivity to light in the sea-anemone *Metridium senile* (L): Adaptation and action spectra. *Proceedings of the Royal Society of London* **148**, 385–396.
Ooka, S., Katow, T., Yaguchi, S., Yaguchi, J. & Katow, H. (2010). Spatiotemporal expression pattern of an encephalopsin orthologue of the sea urchin *Hemicentrotus pulcherrimus* during early development, and its potential role in larval vertical migration. *Development, Growth & Differentiation* **52**, 195–207.
Oshima, N. (2001). Direct reception of light by chromatophores of lower vertebrates. *Pigment Cell Research* **14**, 312–319.
Packard, A. & Brancato, D. (1993). Some responses of *Octopus* chromatophores to light. *Journal of Physiology* **459**, 429.
Panda, S., Sato, T., Castrucci, A., Rollag, M., Degrip, W., Hogenesch, J., Provencio, I. & Kay, S. (2002). Melanopsin (Opn4) requirement for normal light-induced circadian phase shifting. *Science* **298**, 2213–2216.
Pankey, S., Sunada, H., Horikoshi, T. & Sakakibara, M. (2010). Cyclic nucleotide-gated channels are involved in phototransduction of dermal photoreceptors in *Lymnaea stagnalis*. *Journal of Comparative Physiology B: Biochemical, Systemic, and Environmental Physiology* **180**, 1205–1211.
Passano, L. & Mccullough, C. (1962). The light response and the rhythmic potentials of *Hydra*. *Proceedings of the National Academy of Sciences of the United States of America* **48**, 1376–1382.
Pearse, V.B. (1974). Modification of sea anemone behavior by symbiotic zooxanthellae: Expansion and contraction. *Biological Bulletin* **147**, 641–651.
Plachetzki, D.C., Fong, C.R. & Oakley, T.H. (2010). The evolution of phototransduction from an ancestral cyclic nucleotide gated pathway.

Proceedings of the Royal Society B: Biological Sciences **277**, 1963–1969.

Plachetzki, D.C., Degnan, BM. & Oakley, TH. (2007). The Origins of Novel Protein Interactions during Animal Opsin Evolution. *PLoS ONE* **2**(10): e1054. doi:10.1371/journal.pone.0001054.

Provencio, I., Rodriguez, I. & Jiang, G. (2000). A novel human opsin in the inner retina. *Journal of Neuroscience* **20**, 600–605.

Raible, F., Tessmar-Raible, K., Arboleda, E., Kaller, T., Bork, P., Arendt, D. & Arnone, M. (2006). Opsins and clusters of sensory G-protein-coupled receptors in the sea urchin genome. *Developmental Biology* **300**, 461–475.

Richter, S., Loesel, R., Purschke, G., Schmidt-Rhaesa, A., Scholtz, G., Stach, T., Vogt, L., Wanninger, A., Brenneis, G., Doering, C., Faller, S., Fritsch, M., Grobe, P., Heuer, C.M., Kaul, S., Moller, O.S., Mueller, C.H.G., Rieger, V., Rothe, B.H., Stegner, M.E.J. & Harzsch, S. (2010). Invertebrate neurophylogeny: Suggested terms and definitions for a neuroanatomical glossary. *Frontiers in Zoology* **7**, 29.

Röhlich, P., Aros, B. & Viragh, S. (1970). Fine structure of photoreceptor cells in the earthworm, *Lumbricus terrestris*. *Cell and Tissue Research* **104**, 345–357.

Rubin, E.B., Shemesh, Y., Cohen, M., Elgavish, S., Robertson, H.M. & Bloch, G. (2006). Molecular and phylogenetic analyses reveal mammalian-like clockwork in the honey bee (*Apis mellifera*) and shed new light on the molecular evolution of the circadian clock. *Genome Research* **16**, 1352–1365.

Ruiz, M. & Anadon, R. (1991). Some considerations on the fine structure of rhabdomeric photoreceptors in the amphioxus, *Branchiostoma lanceolatum* (Cephalochordata). *Journal für Hirnforschung* **32**, 159–164.

Rushforth, N., Burnett, A. & Maynard, R. (1963). Behavior in hydra: Contraction responses of *Hydra pirardi* to mechanical and light stimuli. *Science* **139**, 760–761.

Sakakibara, M., Aritaka, T., Iizuka, A., Suzuki, H., Horikoshi, T. & Lukowiak, K. (2005). Electrophysiological responses to light of neurons in the eye and statocyst of *Lymnaea stagnalis*. *Journal of Neurophysiology* **93**, 493–507.

Salvini-Plawen, L. & Mayr, E. (1977). On the evolution of photoreceptors and eyes. *Evolutionary Biology* **10**, 207–253.

Sawyer, S., Dowse, H. & Shick, J. (1994). Neurophysiological correlates of the behavioral response to light in the sea anemone *Anthopleura elegantissima*. *Biological Bulletin* **186**, 195–201.

Shick, J. & Dykens, J.A. (1984). Photobiology of the symbiotic sea anemone *Anthopleura elegantissima*: Photosynthesis, respiration, and behavior under intertidal conditions. *The Biological Bulletin* **166**, 608–619.

Siddiqui, I. & Viglierchio, D. (1970). Ultrastructure of photoreceptors in the marine nematode *Deontostoma californicum*. *Journal of Ultrastructure Research* **32**, 558–571.

Singla, C. (1974). Ocelli of hydromedusae. *Cell and Tissue Research* **149**, 413–429.

Speiser, D.I., Eernisse, D.J. & Johnsen, S. (2011). A chiton uses aragonite lenses to form images. *Current Biology* **21**, 665–670.

Steven, D. (1963). The dermal light sense. *Biological Reviews* **38**, 204–240.

Stoll, C. (1972). Sensory systems involved in shadow response of *Lymnaea stagnalis* (L) as studied with use of habituation phenomena. *Proceedings of the Koninklijke Nederlandse Akademie van Wetenschappen Series C: Biological and Medical Sciences* **75**, 342–351.

Stoll, C. (1976). Extraocular photoreception in *Lymnaea Stagnalis* L. In *Neurobiology of Invertebrates, Gastropoda Brain*. ed. Salánki, J. Akadémiai Kiadó, location: Budapest pp 487–495

Su, C., Luo, D., Terakita, A., Shichida, Y., Liao, H., Kazmi, M., Sakmar, T. & Yau, K. (2006). Parietal-eye phototransduction components and their potential evolutionary implications. *Science* **311**, 1617–1621.

Suga, H., Schmid, V. & Gehring, W. (2008). Evolution and functional diversity of jellyfish opsins. *Current Biology* **18**, 51–55.

Tardent, P. & Frei, E. (1969). Reaction patterns of dark and light adapted *Hydra* to light stimuli. *Cellular and Molecular Life Sciences* **25**, 265–267.

Tarttelin, E., Bellingham, J., Hankins, M., Foster, R. & Lucas, R.J. (2003). Neuropsin (Opn5): A novel opsin identified in mammalian neural tissue. *FEBS Letters* **554**, 410–416.

Tong, D., Rozas, N., Oakley, T., Mitchell, J., Colley, N.J. & Mc Fall-Ngai, M.J. (2009). Evidence for light perception in a bioluminescent organ. *Proceedings of the National Academy of Sciences* **106**, 9836–9841.

Ullrich-Lüter, E.M., Dupont, S., Arboleda, E., Hausen, H., Arnone, MI. (2011). Unique system of photoreceptors in sea urchin tube feet. *Proceedings of the National Academy of Sciences of the United States of America*, 10.1073/pnas.1018495108.

Ward, A., Liu, J., Feng, Z. & Xu, X. (2008). Light-sensitive neurons and channels mediate phototaxis in C. *elegans*. *Nature Neuroscience* **11**, 916–922.

Watson, G. & Hessinger, D. (1989). Cnidocyte mechanoreceptors are tuned to the movements of swimming prey by chemoreceptors. *Science* **243**, 1589–1591.

Watson, G. & Hessinger, D. (1994). Evidence for calcium channels involved in regulating nematocyst discharge. *Comparative Biochemistry and Physiology* **107**, 473–481.

Wiederhold, M., JR, E.M. & Bell, A. (1973). Photoreceptor spike responses in the hardshell clam, *Mercenaria mercenaria*. *Journal of General Physiology* **61**, 24–55.

Wilkens, L. & Larimer, J. (1972). The CNS photoreceptor of crayfish: Morphology and synaptic activity. *Journal of Comparative Physiology A: Neuroethology, Sensory, Neural, and Behavioral Physiology* **80**, 389–407.

Woodley, J. (1982). Photosensitivity in *Diadema antillarum:* Does it show scototaxis? In *Echinoderms, Proceedings of the International Conference, Tampa Bay*. ed. Lawrence, J.M., pp. 61: CRC Press A.A. Balkema, Rotterdam.

Xiang, Y., Yuan, Q., Vogt, N., Looger, L.L., Jan, L.Y. & Jan, Y.N. (2010). Light-avoidance-mediating photoreceptors tile the *Drosophila* larval body wall. *Nature* **468**, 921–926.

Yamasu, T. & Yoshida, M. (1973). Electron microscopy on the photoreceptors of the anthomedusae and a scyphomedusa. *Publications. Seto Marine Biological Laboratory, Kyoto University* **20**, 757–778.

Yanase, T. & Sakamoto, S. (1965). Fine structure of the visual cells of the dorsal eye in molluscan *Onchidium verruculatum*. *Zoological Magazine* **74**, 238–242.

Yerramilli, D. & Johnsen, S. (2010). Spatial vision in the purple sea urchin *Strongylocentrotus purpuratus* (Echinoidea). *Journal of Experimental Biology* **213**, 249–255.

Yoshida, M. (1979). Extraocular photoreception. In *Handbook of Sensory Physiology*, **vol. 7**, ed. Autrum, H., pp. 581–640. Berlin: Springer.

Zylstra, U. (1971). Distribution and ultrastructure of epidermal sensory cells in the freshwater snails *Lymnaea stagnalis* and *Biomphalaria pfeifferi*. *Netherlands Journal of Zoology* **22**, 283–298.