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Enlightening the brain: Linking deep brain photoreception with behavior and physiology

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Abstract

Vertebrates respond to light with more than just their eyes. In this article we speculate on the intriguing possibility that a link remains between non-visual opsins and neurohormonal systems that control neuronal circuit formation and activity in mammals. Historically, the retina and pineal gland were considered the only significant light-sensing tissues in vertebrates. However, over the last century evidence has accumulated arguing that extra-ocular tissues in vertebrates influence behavior through non-image-forming photoreception. One such class of extra-ocular light detectors are the long mysterious deep brain photoreceptors. Here we review recent findings on the cellular identity and the function of deep brain photoreceptors controlling behavior and physiology in zebrafish, and discuss their implications.

Keywords

behavior; deep brain photoreceptors; melanopsin; neurohormones; zebrafish

Introduction: Extra-retinal photoreceptors in the vertebrate brain

Light plays a central role in modulating the behavior and physiology of most animals. Many species possess a structure similar to the vertebrate retina that has a specialized function for image-forming vision in which both spectral and temporospatial patterns of light are differentiated. However, other forms of photoreception that do not involve image-forming vision are also common, including measures of irradiance, direction of illumination and light polarization. Over the last century evidence has accumulated that extra-retinal tissues in vertebrates influence behavior through non-image-forming photoreception. Extra-retinal photoreception has been best characterized in non-mammalian vertebrates and occurs at several sites, including the pineal complex and by so-called “deep brain” photoreceptors. Pineal photoreception was shown to significantly contribute to circadian regulation (reviewed in [1]) and several opsins are expressed within the pineal complex [2]. However, the identity and function of deep brain photoreceptors has remained a mystery [3]. More

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than one hundred years ago, Karl von Frisch demonstrated that blind, pinealectomized European minnows retained the ability to alter skin pigmentation in response to illumination of the head, leading him to postulate the existence of photoreceptive cells in the brain itself [4]. Little attention was paid to this finding until several decades later when evidence mounted suggesting that deep brain photoreception may be common in non-mammalian vertebrates [5]. Recent work in zebrafish has finally revealed the molecular identity, location and behavioral function of one population of deep brain photoreceptors [6]. Here we review behavioral functions of deep brain photoreceptors and outline the hypothesis that these neurons represent an ancestral cell type with both sensory and neurosecretory functions [7]. Based on this idea, we suggest that the evolutionary history of non-visual photoreception helps to explain recent findings that non-visual opsins regulate the development and function of photoreception in mammals.

The cellular identity and behavioral function of non-visual photoreceptors

Analysis of opsin expression in zebrafish led to the surprising conclusion that opsins and photosensitive cells are present in many regions of the brain and in several non-neuronal tissues [2, 6–8] (Fig. 1). One such opsin, *tmtopsa*, is expressed in cells throughout the brain, heart and kidney tissues [2, 7]. The presence of *tmtopsa* in the viscera may be due to a role in the regulation of peripheral circadian clocks [8], a plausible hypothesis as many zebrafish tissues respond directly to light and are thought to have endogenous circadian oscillators [9]. The ability of single cells to detect light and trigger light-dark cycles may represent an evolutionary ancient capability that precedes the centralization of circadian regulation by discrete brain nuclei.

A well-established role for extra-retinal photoreceptors is in regulating skin pigmentation. Zebrafish have at least two mechanisms for regulating skin color. First, a retinal or pineal dependent pathway that matches skin pigmentation to environmental background (the ‘camouflage response’) [10]. A second pathway is mediated by yet unknown photoreceptors in the tail that trigger skin darkening in response to illumination [11]. As this second pathway predominates in pre-hatching larvae, it has been speculated that the darkening response may protect against damaging UV light exposure at stages where larvae have limited mobility. Extra-retinal photoreception has also been linked to the regulation of behavior. Pre-hatching larvae show a vigorous ‘photomotor response’ when exposed to intense light [12]. The photomotor response is observed before retinal ganglion cell projections exit the eye and is mediated by as yet unidentified photosensitive neurons within the hindbrain [12]. As this behavior is manifest while larvae are still enclosed in their chorion, its adaptive value is unknown. A clue is that this response is present only during a narrow time window [12] suggestive of a critical developmental period for neural plasticity. One possibility is thus that during the photomotor response light triggers synchronous activation of cells in the motor system to facilitate competition for the acquisition of synaptic partners.

Our own recent work has identified a group of photosensitive neurons that control ‘dark photokinesis’ - an increase in locomotor activity triggered by a reduction in ambient light intensity [6]. This behavior does not require the eyes or the pineal but rather hypothalamic

deep brain photoreceptor cells which depend on the Otp transcription factor and express melanopsin (*opn4a*) [6]. Dark photokinesis was sensitized when *opn4* was selectively overexpressed in a small group of cells including those in the anterior preoptic region that we identified as deep brain photoreceptors. Why would a non-visual mechanism drive hyperactivity in response to darkness? We speculate that this behavior represents an ancient, non-directional mechanism for light-seeking that enables larvae to rapidly move out of dark environments where there is insufficient light for retinal cone photoreceptors to control rapid visual behaviors like hunting or predator avoidance (Fig. 2). Melanopsin expressing photoreceptors integrate light over much longer time frames than classical photoreceptors [3] and are thus well suited for controlling a relatively slow onset, but long lasting behavior like dark photokinesis. As simple detection of irradiance does not require the high spatial resolution provided by the lens-retina system, there would be little selective pressure for the role of deep brain photoreceptors to be subsumed by the retina, perhaps explaining the persistence of these cells in animals with well-developed eyes. While one behavioral role of preoptic melanopsin expressing neurons is now apparent, the unexpected finding that many opsins show patterned expression within the brain has generated a whole new set of questions. Do these potentially light sensing proteins truly act as photoreceptors, and if so, by what mechanisms do they influence physiology and behavior? A clue is offered by the intriguing nexus between opsin expressing cells and the neurohormonal system.

Links between deep brain photoreceptors and the neurohormonal system

Several lines of evidence suggest that at least in some cases, deep brain photoreceptor cells may share the unique feature of contacting the cerebrospinal fluid (CSF) [7, 13]. Interestingly, CSF-contacting neurons structurally resemble modified pineal photoreceptors, and are the dominant neuronal population of the intrapineal region [14]. Cells of the pineal organ in vertebrates act like a “photoneuroendocrine unit”, translating light stimuli into a neuroendocrine response, consisting of melatonin biosynthesis and its release into the cerebrospinal fluid [15, 16]. Similarly, CSF-contacting neurons can signal both through synaptic and non-synaptic mechanisms and are frequently connected with the neurosecretory system [13]. Supporting the idea of a close connection between deep brain photoreceptors and the neurohormonal system, work in zebrafish has shown that *tmt-opsin* expressing neurons in the hypothalamus coexpress vasotocinergic markers [7]. Also, common evolutionarily ancient mechanisms control the differentiation of several neurohormonal cell types as well as melanopsin expressing cells in a hypothalamic domain defined by the transcription factors Orthopedia and the Arnt2/Sim1 heterodimer [6, 17]. A proto-hypothalamoretinal territory is present in ascidians, where larval dopaminergic cells derive from an ancestral, multifunctional cell population located in a photoreceptive field [18]. Together, these findings support the existence of a potential direct connection between photoreceptive opsin-expressing neurons and neurosecretory cells or even cells with a dual photoreceptive-neurosecretory character. Indeed, it has been hypothesized that a minimal regulatory unit combining both sensory and neurosecretory functions in a single cell was present in early bilaterians, these functions being segregated through evolution into distinct but connected neurons [7]. What behavioral role could light-sensitive neurosecretory cells play? An intriguing possibility is that these cells are responsible for the tuning of arousal

state by illumination intensity. In zebrafish, loss of illumination triggers a period of hyperactivity followed by a gradual reduction in activity until larvae enter a sleep-like state [19]. The acute regulation of activity levels by light ('locomotor masking') also occurs in mammals (reviewed in [20]) and is impaired in melanopsin knockout mice [21]. Masking is intact after pineal ablation and enucleation in zebrafish, suggesting that this behavior is also mediated by deep brain photoreceptors and could also occur via melanopsin activation (Fero and Burgess unpublished observations). In the posterior tuberculum, some *opn4a* expressing neurons are part of dopaminergic cell clusters which are known to form long-range projections to the hindbrain and spinal cord [22], suggesting that they may directly be involved in modulating locomotion. Interestingly, this is similar to some photoreceptor cells of the pineal in teleosts that possess long-range projections and may propagate graded potentials over long distances [14]. Thus deep brain photoreceptors may represent an ancestral state of photoreception and at least in some cases, regulate behavior by directly secreting neuromodulatory molecules. Studies that examine how diencephalic photoreceptors signal changes in light conditions to downstream circuits are a promising line of investigation to test this idea.

Non-visual photoreception in mammals

Fish are not the only vertebrates to utilize extra-retinal light perception. There is strong evidence that amphibians, reptiles and birds all possess functional photoreceptors outside the retina (reviewed in [3]). In mammals, melanopsin mediates the intrinsic photosensitivity of the iris [23] but evidence for true deep brain photoreception is largely circumstantial. Characteristic features of the mammalian retina appear to have been acquired during the Mesozoic Era when early mammals adopted a nocturnal lifestyle [24]. It has been proposed that during this 'nocturnal bottleneck', deep brain photoreceptors moved into the retina to maximize light sensitivity in poorly lit environments [24]. However we suggest that vestiges of non-visual photoreception remain in mammals where they influence behavior through several mechanisms.

First, there is evidence that light can effect mammalian brain physiology independent of retinal function [25]. This includes the finding that enucleation in rats does not eliminate negative phototaxis [26], a behavior that is melanopsin dependent in mice [27]. As opsins are known to be expressed in the mammalian brain [28] and significant amounts of light penetrate through the skull and epidermis of newborn rodents [25] it is possible that deep brain photoreception retains a physiological role in mammals. Second, non-visual photoreception may influence developmental processes in mammals. In amphibians environmental illumination dynamically regulates the differentiation of dopaminergic neurons [29], and similarly, light penetrates through the visceral cavity of a pregnant mouse to influence fetal retinal development via melanopsin [30]. Potential roles in neural development may have also maintained deep brain photoreception throughout evolution by effectively uncoupling the central roles of light in maturation of the nervous system from the slow development of the increasingly complex retinal vision. Finally, there are strong indications that the association of melanopsin photoreceptor cells with neuromodulatory cells in lower vertebrates is mirrored in mammals. Melanopsin-based phototransduction drives sustained light responses in retinal dopaminergic neurons [31]. Dopaminergic

amacrine neurons are a central neuromodulatory system of the retina, reconfiguring retinal circuits according to existing illumination conditions. In addition, recent work has shown that abnormal light rhythms can negatively affect mood through a melanopsin dependent pathway [32] and has linked melanopsin gene variants to increased risk of seasonal affective disorder [33]. These findings suggest that in mammals, melanopsin expressing cells are primarily situated in the retina, but have maintained their connection with neuroendocrine cells for the control of mood. This connection may have an ancestral state where deep brain photoreceptors were closely associated with neurohormonal systems.

Conclusions and prospects

Behavioral and genetic experiments performed with zebrafish have confirmed the existence of deep brain photoreceptors. Molecular studies indicate that photosensitive cells may be surprisingly abundant in the zebrafish brain and directly connect with neurohormonal systems controlling physiology and behavior. The nature and function of most of these cells remains almost entirely a mystery. Classical genetic experiments in zebrafish, complemented by new optogenetic technologies for manipulating and monitoring neuronal activity in vivo, offer an exciting opportunity to tackle this puzzle. Understanding how photoreceptive cells in the brain connect to circuits controlling aspects of mood and behavior will provide a fascinating perspective on how photoreception evolved from a simple mechanism for detecting changes in irradiance into the sophisticated system for image-forming vision that is a primary sensory modality for guiding behavior in almost all vertebrate species.

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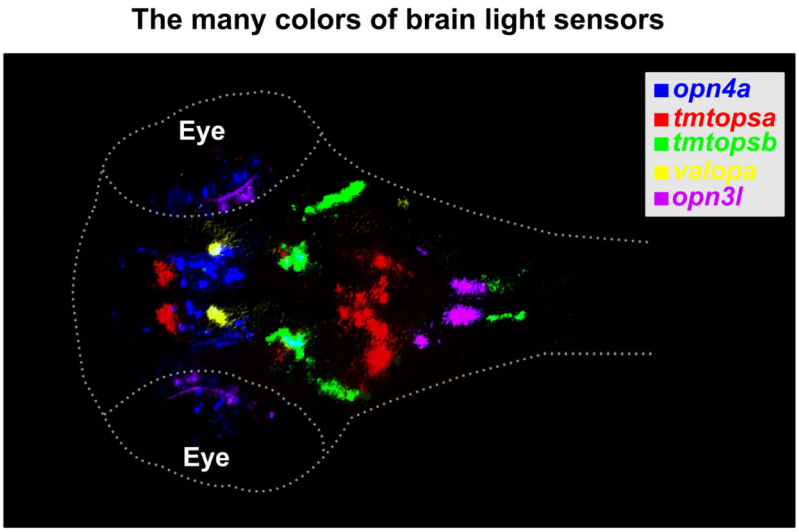

Figure 1.

Non-visual opsins are broadly expressed in the zebrafish central nervous system. Schematic representation showing the expression domains of several non-visual opsins in the brain. Expression is based on whole-mount *in situ* data from *opn4a*, *valopa*, *tmtopsa*, *tmtopsb* and *opn3l* opsins (see colored labels). Data from different WT larvae at 3 days post-fertilization were superimposed.

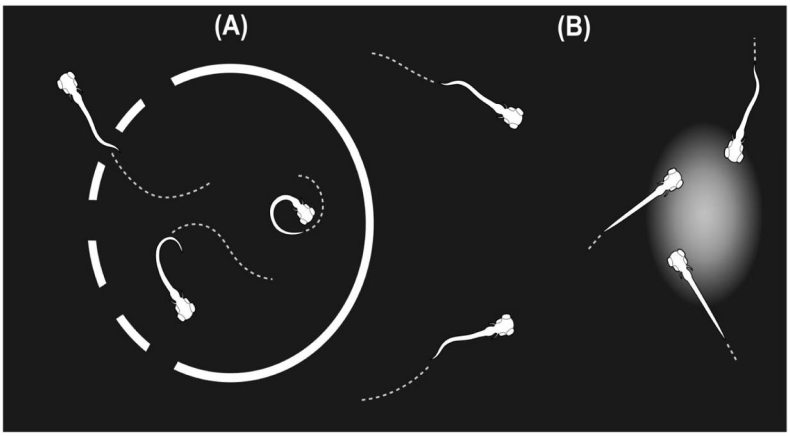

Figure 2.

Illustration of dark photokinesis as a non-directional mechanism for light seeking. **A:** Larvae within an arena are suddenly exposed to complete darkness and are blocked from view of a distant light source. Activity rapidly increases in the dark (dark photokinesis) enabling larvae to eventually escape the arena. **B:** Once outside the arena, the light source becomes visible and larvae use retinal vision to orient and move directly towards the light source.