

## Extraocular Photoreception and Circadian Entrainment in Nonmammalian Vertebrates

Cristiano Bertolucci and Augusto Foà\*

Dipartimento di Biologia and Centro di Neuroscienze,  
Università degli Studi di Ferrara, Ferrara, Italy

### ABSTRACT

In mammals both the regulation of circadian rhythms and photoperiodic responses depend exclusively upon photic information provided by the lateral eyes; however, nonmammalian vertebrates can also rely on multiple extraocular photoreceptors to perform the same tasks. Extraocular photoreceptors include deep brain photoreceptors located in several distinct brain sites and the pineal complex, involving intracranial (pineal and parapineal) and extracranial (frontal organ and parietal eye) components. This review updates the research field of the most recent acquisitions concerning the roles of extraocular photoreceptors on circadian physiology and behavior, particularly photic entrainment and sun compass orientation.

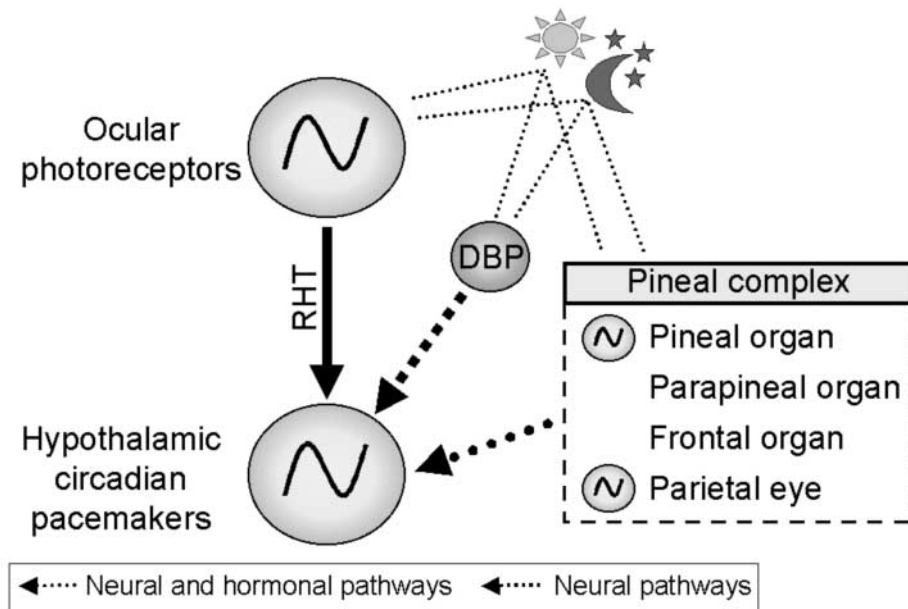
*Key Words:* Circadian; Orientation; Entrainment; Extraocular; Photoreceptor; Vertebrates; Pineal complex.

---

\*Correspondence: Augusto Foà, Ph.D., Dipartimento di Biologia, Università degli Studi di Ferrara, Via L. Borsari, Ferrara 46-44100, Italy; Fax: +39-532-207143; E-mail: foa@unife.it.

INTRODUCTION

In mammals either image detection (vision) or irradiance detection mediating entrainment of circadian rhythms depends upon photic information provided exclusively by the lateral eyes. However, nonmammalian vertebrates can also rely upon multiple, extraocular photoreceptors to mediate irradiance detection tasks (Figure 1). Extraocular photoreceptors, mostly developing from the forebrain, are classified as pineal complex and deep brain photoreceptors. The pineal complex consists of the (1) intracranial pineal organ or pineal body (*epiphysis cerebri*); (2) intracranial parapineal organ found in lampreys and teleost fish; (3) extracranial “third eye,” named frontal organ (or *Stirnorgan*) in anuran amphibians and parietal eye in the *Sphenodon* and lizards. The pineal body is derived embryologically as an evagination of the roof of the diencephalon and, with few exceptions, is ubiquitous in vertebrates. The parapineal organ, frontal organ, and parietal eye either arise as an evagination from the pineal body or as a separate diverticulum from the diencephalon. Deep brain photoreceptors are located in several distinct sites of the brain. The present review focuses on the role(s) of extraocular photoreceptors in circadian physiology and behavior, particularly photic entrainment and time- compensated sun compass. In addition, attention is given to noncircadian aspects.



**Figure 1.** Schematic representation illustrating ocular and extraocular photoreceptive structures involved in the vertebrate circadian system. Arrows indicate pathways between circadian oscillators and photoreceptors. DBP: deep brain photoreceptors; RHT: retino-hypothalamic tract.



## PINEAL

A functional pineal body is present in almost all vertebrates, with the exception of the alligator *Alligator mississippiensis* and the owl *Strix uralensis*, which possess only a very rudimentary pineal (Roth et al., 1980; Taniguchi et al., 1993). In the Agnatha *Mixine glutinosa* the pineal is absent (Vigh-Teichmann et al., 1984).

The pineal is directly photosensitive, containing photoreceptor cells resembling those of the lateral eyes, with well-developed inner and outer segments and presynaptic processes (Korf et al., 1998). The initial characterization of pineal photopigments used immunocytochemistry to demonstrate opsin-like immunoreactivity. Classical visual cone- and rod-like opsins have been localized in pineal photoreceptors of different vertebrate classes (Vigh et al., 2002). For instance, in three anuran amphibians (*Rana catesbeiana*, *Rana nigromaculata*, and *Bufo japonicus*) pinealocytes have been immunolabeled with antiserum against rhodopsin (Okano et al., 2000). Recently, detailed molecular studies discovered novel pineal opsins that are distinct from the classical visual opsin (Table 1). A nonvisual opsin, named pinopsin has been isolated for the first time in the chicken pineal (Okano et al., 1994). Pinopsins have also been isolated from the pineal of the pigeon *Columba livia*, the lizard *Anolis carolinensis*, and the toad *Bufo japonicus* (Kawamura and Yokoyama, 1996, 1997; Okano et al., 1997; Yoshikawa et al., 1998). By immunocytochemistry, pinopsin expression has been detected in the pineal of both diurnal (*Phelsuma madagascariensis longinsulae*) and nocturnal (*Gekko japonicus*) geckos, and in the diurnal lizard *Takydromus tachydromoides* (Taniguchi et al., 2001; Yoshikawa et al., 2001).

Pinopsin has never been detected in the genome of fish and mammals. Alternatively, different kinds of opsin genes have been discovered in the pineal of teleosts (Table 1). For instance, vertebrate ancient (VA) opsin is present in the pineal of Atlantic salmon (*Salmo salar*), carp (*Cyprinus carpio*), and zebrafish (*Danio rerio*) (Kojima et al., 2000; Moutsaki et al., 2000; Philp et al., 2000b). A rod-like opsin has been cloned from the zebrafish, salmon, and pufferfish (*Takifugu rubripes*), (Mano et al., 1999; Philp et al., 2000a). This opsin, named extra-retinal rod-like opsin (ERrod-like opsin), is expressed uniquely in the pineal and shares only 74% identity with the rod-opsins from the retina of the same species (Philp et al., 2000a). An opsin assigned to the pinopsin family has been isolated from the pineal of the marine lamprey *Petromyzon marinus* (Yokoyama and Zhang, 1997). Based upon the level of amino acid identity, genomic structure, and nucleotide phylogeny between lamprey pinopsin and VA opsin, Moutsaki et al. (2000) suggested reassigning the lamprey pinopsin to the VA opsin family. Due to the phylogenetic position of lampreys, lamprey pinopsin has been proposed as the evolutionary precursor of the teleost VA opsin family (Moutsaki et al., 2000). The variation found in the expression and number of photopigments reported above is likely to be related to the fact that fish have adapted to almost every niche in the hydrosphere, ranging from the ocean depths where no light penetrates, to the photic zone near the surface.

Pineal photoreceptors possess secretory activity; they make the hormone melatonin. Melatonin is synthesized from the amino acid tryptophan through a well-known biosynthetic pathway. Melatonin production is confined to the dark portion of a light-dark (LD) cycle and provides a chemical signal that plays an



**Table 1.** Opsins isolated and/or detected by in situ hybridization or immunocytochemistry with specific antiserum from extraocular photoreceptive structures.

Pineal	Pinopsin	Birds	<i>G. domesticus</i>	Okano et al., 1994	
			<i>C. livia</i>		
		Reptiles	<i>A. carolinensis</i>	Kawamura and Yokoyama, 1997	
			<i>P. m. longinsulae</i>	Taniguchi et al., 2001	
			<i>G. japonicus</i>		
			<i>T. tachydromoides</i>		
	VA opsin	Amphibians	<i>B. japonicus</i>	Yoshikawa et al., 1998	
		Lampreys	<i>P. marinus</i>	Yokoyama and Zhang, 1997	
		Teleosts	<i>S. salar</i>	Kojima et al., 2000	
		<i>C. carpio</i>	Moutsaki et al., 2000		
ERrod-like opsin	Teleosts	<i>D. rerio</i>	Philp et al., 2000		
		<i>S. salar</i>	Philp et al., 2000		
		<i>D. rerio</i>	Mano et al., 1999		
		<i>T. rubripes</i>			
Parapineal	Parapinopsin	Teleosts	<i>I. punctatus</i>	Blackshaw and Snyder, 1997	
Parietal eye	Pinopsin	Reptiles	<i>A. carolinensis</i>	Kawamura and Yokoyama, 1997	
Deep brain	Melanopsin	Amphibians	<i>X. laevis</i>	Provencio et al., 1998	
			<i>D. rerio</i>	Bellingham et al., 2002	
		Teleosts	<i>G. morhua</i>	Drivenes et al., 2003	
	Pinopsin VA opsin (different isoforms)	Amphibians	<i>B. japonicus</i>	Yoshikawa et al., 1998	
		Teleosts	<i>S. salar</i>	Philp et al., 2000	
			<i>D. rerio</i>	Kojima et al., 2000	
				<i>C. carpio</i>	Moutsaki et al., 2000
				<i>P. altivelis</i>	Minamoto and Shimizu, 2002
		Rhodopsin	Birds	<i>C. livia</i>	Wada et al., 1998
			Teleosts	<i>P. altivelis</i>	Masuda et al., 2003
RH2 opsin	Reptiles	<i>P. sicula</i>	Pasqualetti et al., 2003		
tmt-opsin	Teleosts	<i>D. rerio</i>	Moutsaki et al., 2003		

important role in the regulation of circadian and/or photoperiodic behaviors (Tosini et al., 2001; Underwood and Groos, 1982; Underwood, 1990). Circumstantial evidence suggests that pineal melatonin also plays a role in regulating dermal color changes in fish and amphibians (Aspengren et al., 2003; Daniolos et al., 1990). The lamprey *P. marinus* possesses a well-differentiated photosensitive pineal that controls the circadian rhythm of melatonin synthesis (Bolliet et al., 1993). Because of the poor development of their eyes (de Miguel et al., 1990), *P. marinus* larvae use pineals as their main photoreceptive organs (Yanez et al., 1993). Furthermore, in *Lampetra fluviatilis* the pineal controls changes in body coloration, metamorphosis, and photoperiodic sexual maturation (Cole and Youson, 1981; Jones 1973b; Joss, 1973a).



Entrainment of the circadian activity rhythms to a LD cycle in *Lampetra japonica* is pineal-dependent (Morita et al., 1992).

In isolated cultured pineals of teleosts, melatonin synthesis is rhythmic under LD conditions, with the rhythm persisting for several days in constant conditions in some, but not all species investigated (Bolliet et al., 1996; Cahill, 2002). For instance, the trout pineal produces melatonin rhythmically in vitro in LD, whereas it synthesizes melatonin at high constant levels when cultured in constant darkness (DD) (Coon et al., 1998; Max and Menaker, 1992). In this teleost, light does not entrain circadian oscillators coupled to melatonin synthesis but acts directly on the pineal to suppress melatonin during daytime (Coon et al., 1998). The role of the pineal in the control of circadian behavioral rhythms has been studied in different teleosts. Ablation of the pineal in several species can induce arrhythmicity or changes in the length of the freerunning period. For instance, in the catfish *Heteropneustes fossilis* pinealectomy abolishes locomotor activity rhythms in DD (Garg and Sundararaj, 1986). However, many investigations have showed the pineal is not necessary for the photic entrainment: pinealectomized fish are still entrainable to LD cycles. In some fish pineal photoreception plays an important role during embryonic and larval life stages, especially during times when the retina does not yet possess corresponding photoreceptor capacity. For instance, in embryos and early larvae of the Atlantic halibut *Hippoglossus hippoglossus* the only differentiated photoreceptor organ at those life stages is the pineal, with light sensitivity for short (UV), and middle (green) wavelengths (Forsell et al., 2002). Pineals of amphibians synthesize melatonin rhythmically in vivo (Korf et al., 1998). *Xenopus laevis* pineals are also capable of producing melatonin rhythmically in vitro under LD cycles, although these rhythms disappear relatively quickly in DD (Green et al., 1999). Most investigations of amphibian circadian systems have focused on retinal circadian oscillators; relatively little is known about the circadian function of the pineal. Different investigations show that ablation of the *Xenopus* pineal alters circadian activity rhythms, but does not abolish photic entrainment of these rhythms (Cahill, 2002; Harada et al., 1998).

It is well known that amphibians use their circadian clock to compensate for the apparent movement of the sun (Sinsch, 1990). In this way they can perform directional orientation during migration by means of their sun compass. It is noteworthy that pineal photoreceptors of both larval and adult salamanders (*Ambystoma tigrinum*) can perceive the e-vector of plane polarized light and thus determine the sun azimuth under overcast skies. In this way, salamanders can orientate themselves by means of the sun compass also when the sun disk is not directly visible (Taylor and Adler, 1973, 1978). Pineal photoreceptors have also been shown to be involved in noncircadian behavioral tasks, such as magnetic compass orientation. In the eastern red spotted newt (*Notophtalmus viridiscens*), wavelength-dependent effects of light on magnetic compass orientation result from an antagonistic interaction between short ( $\leq 450$  nm) and long-wavelength ( $\leq 500$  nm) photoreception mechanisms (Phillips et al., 2001). Both short- and long-wavelength inputs to the magnetic compass of newts have been shown to be mediated by extraocular photoreceptors located in the pineal, although involvement of deep brain photoreceptors cannot be ruled out (Deutschlander et al., 1999; Phillips et al., 2001). The pineal also plays a central role in the swimming response to dimming of young



*X. laevis* tadpoles. Low ambient light levels can affect the vertical distribution of *Xenopus* tadpoles by influencing their swimming so that they tend to swim upwards. Pinealectomy blocks the responses of tadpoles to dimming (Jamieson and Roberts, 2000). In the future, the possibility of rapid generation of transgenic *Xenopus* targeted to photoreception, melatonin synthesis, orientation, and clock genes expression will be particularly useful in chronobiology.

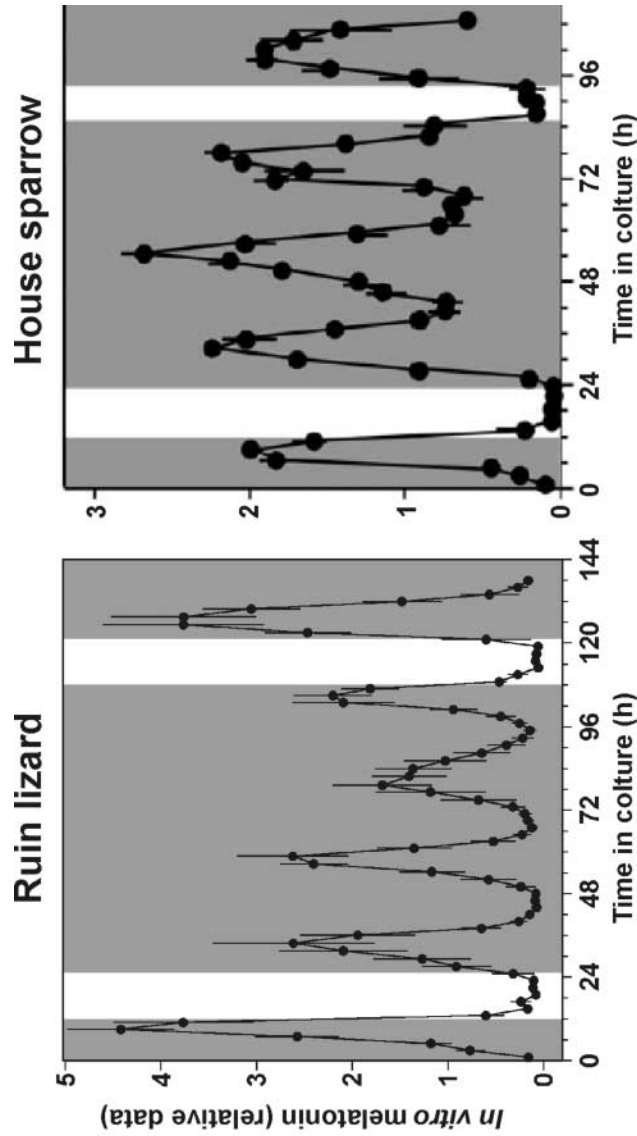
The pineal plays a central role in the regulation of circadian rhythmicity of reptiles (Tosini et al., 2001; Underwood, 1990). The pineal is involved in the generation and control of different circadian rhythms such as locomotor activity, body temperature, behavioral thermoregulation, and electroretinographic responses (Tosini et al., 2001). In all reptile species thus far investigated, the pineal releases melatonin in the blood rhythmically. In most, but not all, species the melatonin rhythm persists also when the animals are kept in DD and constant temperature, thus demonstrating its true circadian nature. The presence of pineal circadian oscillators that control melatonin synthesis *in vitro* have been verified in some lizards, namely *A. carolinensis*, *Sceloporus occidentalis*, *Iguana iguana*, and *Podarcis sicula* (Figure 2), but not in others, such as *Dipsosaurus dorsalis* (Bertolucci et al., 2003; Janik and Menaker, 1990; Menaker and Wisner, 1983; Menaker, 1985; Tosini and Menaker, 1998). No findings indicate the pineal is crucial for photic entrainment of circadian rhythms in reptiles whose lateral eyes have been removed.

The pineal gland of avian species contains circadian oscillators entrainable to LD cycles that produce melatonin in a rhythmic manner (Figure 2) (Brandstätter, 2003). Gwinner and Brandstätter (2001) recently summarized the most relevant data concerning the role of the pineal in the avian circadian system. Remarkably, investigations on the house sparrow (*Passer domesticus*) show day-length information is reflected in the pattern of daily blood melatonin release and retained in the pineal isolated *in vitro*. These data reveal the house sparrow pineal can store and retain biological information about time and can use it to determine increasing/decreasing day lengths (Brandstätter et al., 2000).

### PARAPINEAL ORGANS

In addition to the pineal, lampreys and teleosts possess an intracranial parapineal organ which arises as a dorsal evagination from the diencephalon (Vollrath, 1981). The parapineal is absent in cartilaginous fish (Holocephala, rajids, and sharks). In the Japanese grass lizard *T. tachydromoides*, a parapineal morphologically similar to the pineal gland has been localized below the parietal eye (Yoshikawa et al., 2001). Immunocytochemical analysis documents the existence of rhodopsin-like and pinopsin-like pigments in this reptilian parapineal (Yoshikawa et al., 2001). Fish parapineals contain photoreceptors (Garcia-Fernandez et al., 1997). An opsin has been cloned from the parapineal of channel catfish *Ictalurus punctatus* that defines a new gene family of vertebrate photopigments termed parapinopsin (Table 1) (Blackshaw and Snyder, 1997). Parapinopsin is also strongly expressed in the pineal stalk, while its expression in the pineal is at a lower level (Blackshaw and Snyder, 1997). Molecular phylogenetic analysis suggests that parapinopsin is closely related to the visual pigment *Ci-opsin1*, identified in a





**Figure 2.** In vitro melatonin release in LD and DD from cultured pineals of the ruin lizard and the house sparrow. Profiles of melatonin release demonstrate in both species the existence of pineal circadian oscillators entrainable to LD cycles. Grey bars indicate dark phase of the LD cycles and DD (Right panel from Brandstätter (2003)).



primitive chordate, the ascidian *Ciona intestinalis* (Bellingham and Foster, 2002; Kusakabe et al., 2001). The presence of different kinds of opsins in the pineal and parapineal organs of catfish suggests that they might be specialized to perceive different wavelengths of light. It is unclear whether the parapineal contains circadian oscillators and produces melatonin. However, zebrafish parapineal cells can transcribe in circadian manner: (a) arylalkylamine *N*-acetyltransferase 2 (*Aanat2*); (b) the interphotoreceptor retinoid-binding protein (*Irbp*); and (c) *Rev-erb- $\alpha$* , an orphan nuclear receptor (Gamse et al., 2001).

### FRONTAL ORGAN

In anurans, the pineal complex is composed of the extracranial frontal organ and the intracranial pineal organ. The frontal organ is located between the eyes in a depigmented area. Like the pineal, it contains photoreceptor cells, glial elements, and secondary neurons. The photoreceptors of the frontal organ possess cone-like outer segments and show immunoreactivity for iodopsin and rhodopsin (Masuda et al., 1994; Okano et al., 2000). Morphological and electrophysiological evidence in the frog *Rana esculenta* indicates the frontal organ might represent an autonomic component of the pineal complex with secretory function, since it produces neurohormonal messages involved in the mechanism of annual reproduction (Guglielmotti et al., 1997). Results of studies in which green frogs *Rana clamitans* were deprived of lateral eyes, pineal gland, and frontal organ suggest that the frontal organ, alone, is capable of mediating extraocular photic entrainment (Adler, 1971). Furthermore, there is clear evidence the frontal organ of cricket frogs *Acris gryllus* and bullfrog *Rana catesbeiana* is involved in determining the sun azimuth enabling sun compass orientation (Justis and Taylor, 1976; Taylor and Ferguson, 1970).

### PARIETAL EYE

In reptiles the pineal complex is composed of the intracranial pineal and, in *Sphenodon* and lizards, the extracranial parietal eye. The parietal eye consists of a dorsal lens and ventral retina, both situated below a transparent cornea. The parietal eye retina is very simple. This retina is composed of photoreceptors and ganglion cells only, plus the axons of the ganglion cells form the parietal nerve. The parietal nerve innervates several areas of the brain (thalamic, hypothalamic, and telencephalic regions), but it does not project to the visual region (Engbretson, 1992; Quay, 1979). Very little is known about the function of the parietal eye of lizards. The parietal eye synthesizes melatonin but in much lower quantities than the pineal gland (Tosini and Menaker, 1998). It is likely that melatonin simply fulfills a local function within the parietal eye. Furthermore, Tosini and Menaker (1998) showed that the parietal eye of the *I. iguana* synthesized melatonin in vitro under the control of circadian oscillators. Recently, the parietal eye has become an interesting model to study the evolution of phototransduction mechanisms in vertebrate photoreceptors. In fact, parietal eye photoreceptors depolarize to light under dark-adapted conditions, unlike rods and cones but similar to most invertebrate





photoreceptors (Xiong et al., 1998). The parietal eye exhibits a chromatic response to visible light (Engbretson, 1992; Solessio and Engbretson, 1993, 1999). Maximal spectral sensitivity of electroretinogram responses in the parietal eye of *Xantusia vigilis* is demonstrable for green (495 nm) and blue (430 nm) light (Solessio and Engbretson, 1999). Molecular analysis confirms this range of spectral sensitivity. In *A. carolinensis*, RT-PCR tests reveal the expression of opsins, classified in three different families: short wavelengths (UV/blue opsin), long-middle wavelengths (green/red opsin), and pinopsin (Table 1) (Kawamura and Yokoyama, 1997). Electrophysiological investigations also demonstrate parietal eye unresponsiveness to infrared wavelengths (Miller and Wolbarsht, 1962).

Investigations on *A. carolinensis* and *P. sicula* indicate the parietal eye is not involved in the control of locomotor rhythmicity (Underwood, 1983; Foà, 1991). However, the parietal eye seems to be involved in many physiological functions in lizards, such as thermoregulation and sun compass orientation. For instance, in the ruin lizard *P. sicula* ablation of parietal eye does not affect locomotor rhythmicity but temporarily abolishes the circadian rhythm of behavioral temperature selection (Innocenti et al., 1993). In *I. iguana* parietectomy produces transient increase of body temperature during the first and second night following surgery (Tosini and Menaker, 1996). In general, the evidence that reptile species inhabiting tropical and semi-tropical area lack the parietal eye, whereas those species living in temperate zone possess one supports the hypothesis that the parietal eye is involved in thermoregulation (Gundy et al., 1975).

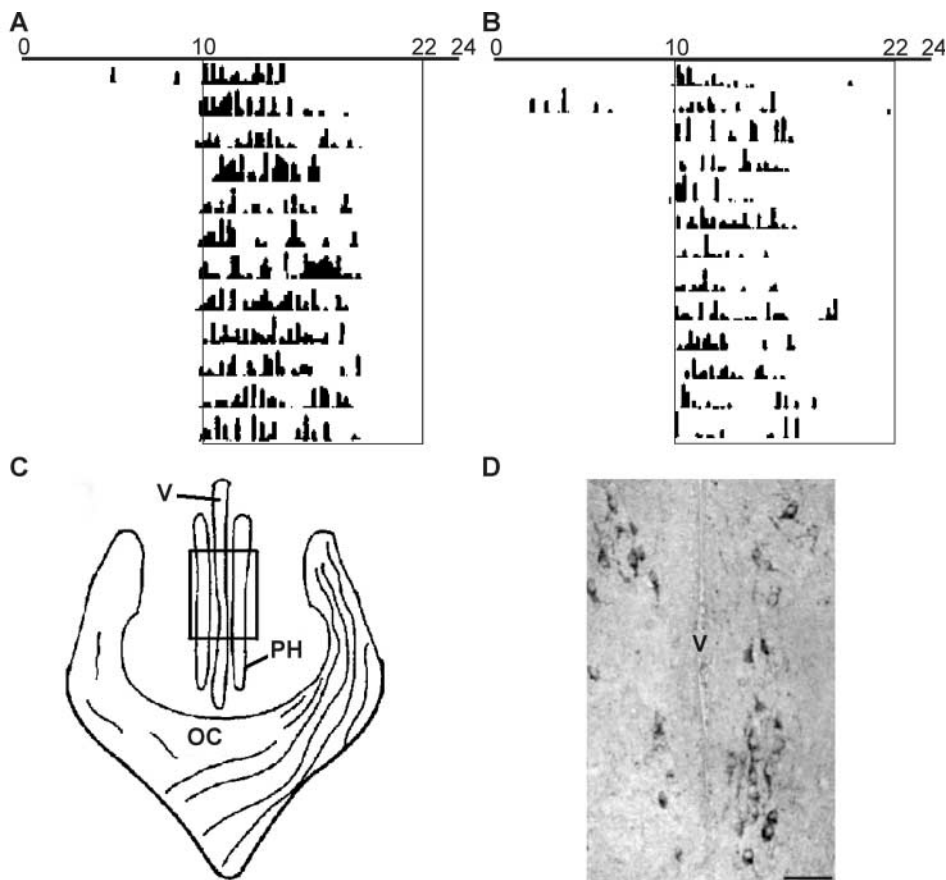
The parietal eye plays a critical role in homing behavior (Bissinger, 1980). Detailed studies have been done on the iguanid lizard *Sceloporus jarrovi* (Ellis-Quinn and Simon, 1991) and Australian sleepy lizard *Tiliqua rugosa* (Freake, 2001). Clock-shift experiments on *S. jarrovi* demonstrate these lizards can use a time-compensated sun compass to orientate themselves in the homeward direction; covering their parietal eye significantly reduces homing performances in comparison to controls. *T. rugosa* displaced away from home and released under the sun oriented at random when the parietal eye was covered, while control lizards with a sham parietal eye patch oriented homeward. Remarkably, in all these studies the lateral eyes were unobstructed and had complete access to visual cues, including celestial cues and landmarks. Collectively, these results suggest the parietal eye plays a highly significant role in mediating sun compass orientation and homing of lizards (Ellis-Quinn and Simon, 1991; Freake, 2001).

## DEEP BRAIN PHOTORECEPTORS

The existence of extraocular photoreceptors located deep in the brain, the so-called deep brain photoreceptors (DBP), has been demonstrated in a broad range of nonmammalian vertebrate species (Foster et al., 1994; Shand and Foster, 1999; Vigh et al., 2002). The earliest evidence of the existence of DBP was provided by von Frisch (1911) and Scharrer (1928) in fish. Further, indications came from experiments on birds. Blinded ducks exposed to winter photoperiods show testis growth if the hypothalamus is directly illuminated with summer photoperiods via small quartz rods (Beinot, 1935). The findings of these preliminary investigations were ignored



until later studies by Menaker on the house sparrow (*Passer domesticus*) which demonstrated the role of encephalic photoreception on the entrainment of circadian rhythms and induction of gonadal growth (Menaker, 1968; Menaker and Keatts, 1968). Later, several investigations showed DBP are essential for the regulation of circadian physiology and detection of seasonal changes in photoperiod. For instance, DBP can mediate entrainment of circadian rhythms of locomotor activity to LD cycles in reptiles (Figure 3A–B) and photoperiodic responses that control seasonal breeding in birds (Foà et al., 1993; Foster and Follett, 1985; Pasqualetti et al., 2003; Underwood and Menaker, 1976).



**Figure 3.** Photoc entrainment in the ruin lizard *Podarcis sicula*. Locomotor records of lizards entrained to a LD cycle either as intact (A) or after combined ablation of the pineal complex and the retinae of the lateral eyes (B). Records are representative examples of the fact that DBP are sufficient to permit photoc entrainment of locomotor behavior. Each horizontal line is a record of one day's activity, and consecutive days are mounted one below the other. Rectangles encompass the light phase of the administered LD cycle. (C) Schematic reconstruction of a transverse brain section at the level of the periventricular area (PH) of the hypothalamus. Square encompasses the area of the PH containing DBP. (D) Frontal sections through the PH showing DBP. Scale bars: 10  $\mu$ m. (C and D from Pasqualetti et al. (2003)).



Several investigations suggest the phototransduction cascade of DBP is similar to those described in retinal and pineal cells (Bellingham and Foster, 2002). Both immunocytochemical and molecular analyses reveal the existence of different types of photopigments in the brain of many vertebrate species (Table 1). Photopigments have been localized in the basal telencephalon, anterior hypothalamus, and subhabenular areas. Furthermore, several reports indicate the existence of at least two types of photoreceptor neurons: cerebrospinal fluid (CSF)-contacting neurons and neurosecretory cells. In amphibians, encephalic neurons expressing opsins are found in the anterior hypothalamus: anterior preoptic area, magnocellular preoptic nucleus, and suprachiasmatic nucleus (SCN) (Okano et al., 2000; Provencio et al., 1998; Yoshikawa et al. 1998, 1994). *Xenopus* melanopsin is localized in neurosecretory cells of the magnocellular preoptic nucleus and SCN, while toad pinopsin is localized in CSF-contacting neurons in the anterior preoptic nucleus of the hypothalamus (Provencio et al., 1998; Yoshikawa et al., 1998). In Agnatha and fish, DBP are present in diencephalic and subhabenular areas (Garcia-Fernandez, 1997; Philp et al., 2000b). VA opsin is expressed in the epithalamic cells of the salmon brain (Philp et al., 2000b). The authors did not establish whether these cells are CSF-contacting neurons or neurosecretory cells. A second isoform of VA opsin, VAL (long) opsin, has been identified in zebrafish and carp (Moutsaki et al., 2000; Kojima et al., 2000). Furthermore, in the zebrafish VAL opsin is expressed in CSF-contacting neurons of the central posterior thalamic nucleus (Kojima et al., 2000). Recently, another VA opsin isoform, VAM opsin, and a rhodopsin have been identified in the brain of the smelt fish *Plecoglossus altivelis* (Masuda et al., 2003; Minamoto and Shimizu, 2002). Melanopsins were cloned in the zebrafish and Atlantic cod *Gadus morhua* (Bellingham et al., 2002; Drivenes et al., 2003). Interestingly, in the cod two different melanopsins (opn4a and opn4b) are separately expressed in the SCN and habenula. The expression of opn4a in the SCN is similar to melanopsin expression found in *Xenopus*. This suggests a conserved role for melanopsin in nonvisual photoreceptive tasks. The expression of the other type of melanopsin (opn4b) in the habenula suggests this brain area may be an additional region that integrates photic cue detection in teleosts (Drivenes et al., 2003). A novel opsin family, teleost multiple tissue (tmt-) opsin, was identified in the zebrafish (Moutsaki et al., 2003). Tmt-opsin is expressed in many nonneural tissues and in all the major divisions of the zebrafish brain (Moutsaki et al., 2003). Tmt-opsin is thought to play a central role in the circadian photic entrainment of zebrafish. In birds, photoreceptive brain areas were localized in the hypothalamus and in the septal and tuberal areas (Foster and Follett, 1985; Silver et al., 1988; Wada et al., 1998). In all avian species, tested photopigments are expressed in CSF-contacting neurons. For instance, rhodopsin expression is detected in CSF-contacting neurons of the pigeon lateral septum (Wada et al., 1998).

Different locations of the DBP have been reported also in different lizard species. In the American iguanid lizards *A. carolinensis* and *I. iguana*, cone-opsin immunopositive cells have been exclusively detected in the basal region of the lateral ventricles (Foster et al., 1993; Grace et al., 1996). In the Japanese grass lizards, *T. tachydromoides* neurons expressing rhodopsin have been localized in the posterior pallial commissure and median eminence (Yoshikawa et al., 2001). In all these species, photoreceptors appear to be of similar shape as CSF-contacting neurons.



In contrast, in the European ruin lizards *P. sicula* the DBP are localized in the periventricular area on the hypothalamus and look to be of similar shape as neurosecretory cells (Fig. 3C–D) (Pasqualetti et al., 2003).

A brain opsin has been cloned for the first time in a reptilian species, *P. sicula* (Table 1). The deduced amino acid sequence yields the highest similarity with the RH2 cluster among vertebrate opsins; it includes a mixture of cone-opsins absorbing in the 470–520 nm range (Yokoyama, 2000). Furthermore, posttranscriptional inactivation experiments of endogenous brain cone-opsins mRNA demonstrate for the first time in a vertebrate that brain cone-opsins of lizards are part of a true circadian brain photoreceptor participating in photic entrainment of behavioral rhythms (Pasqualetti et al., 2003).

### CONCLUSIONS

Overall, it may appear that in nonmammalian vertebrates all photosensory tasks are shared between the lateral eyes detecting images for vision and the extraocular photoreceptors mediating irradiance detection allowing animals, for instance, to entrain circadian rhythms to the day-night cycles of the real world. This, however, is not completely valid. Although the lateral eyes are not necessary for entrainment to the day-night cycle, their presence significantly increases the sensitivity of entrainment, as clearly shown in both birds and lizards (Foà et al., 1993; Menaker, 1972; Underwood, 1973).

In the photosensory tasks that extraocular photoreceptors actually perform there is something more than mere irradiance detection. For instance, the pineal of salamanders, the frontal organ of frogs, and the parietal eye of lizards have been shown to be involved in detecting the horizontal direction of a light source, specifically the azimuth of the sun, a necessary task to orientate by means of a sun compass. Sun azimuth also can be determined under overcast skies by detecting the e-vector of plane polarized light, as for instance the salamander pineal does. Overall sun compass orientation, also classified as photomenotaxis (Fraenkel and Gunn, 1940), results in rather sophisticated behavioral performance by detecting the amount of environmental light (irradiance). Future investigations should explore in greater depth at which level(s) of that complex mechanism the frontal organ, pineal body, and parietal eye effectively participate.

One of the intriguing questions that remains to be answered in this field is why the central nervous system of the same nonmammalian species contains multiple types of photopigments that are expressed in many distinct areas. Roenneberg and Foster (1997) proposed that multiple photopigments, which differ in their spectral responses, can be used to obtain information about spectral changes within the environment. Noteworthy, dawn and dusk are the times of day when both changes in the spectral composition are maximal, and signals to photic entrainment of circadian rhythms are most relevant (Aschoff et al., 1982). Hence, multiple photic channels, each extracting slightly different spectral information from the same light environment, may be used by the circadian system to extract reliable judgements about dawn and/or dusk, with the adaptive significance of entraining very accurately



physiological and behavioral rhythms to that reference phase (Foster and Hankins, 2002; Philp et al., 2000b).

Thus far, there is only one case in which a well localized group of deep brain photoreceptors (DBP) has been shown to directly mediate the photic entrainment of circadian behavioral rhythms. This is evident in the neurosecretory cells, all confined within the periventricular area of the hypothalamus, of the ruin lizard *Podarcis sicula* (Pasqualetti et al., 2003). However, neural pathways from these circadian DBP to the primary pacemaker in the SCN have not yet been demonstrated (Minutini et al., 1995). Future investigations using the combination of behavioral, electrophysiological, and molecular approaches will be necessary to place the various DBP found in nonmammalian vertebrates into the right biological context.

### REFERENCES

- Adler, K. (1993). Pineal end organ: role in extraoptic entrainment of circadian locomotor rhythms in frogs. In: Menaker, M., ed. *Biochronometry*. Washington, DC: U.S. National Academy of Science, 342–350.
- Aschoff, J., Daan, S., Homna, K. I. (1982). Zeitgeber, entrainment, and masking: some unsettled questions. In: Aschoff, J., Daan, S., Groos, G. A., eds. *Vertebrate Circadian System (Structure and Physiology)*. Berlin, Heidelberg, New York: Springer-Verlag, 13–24.
- Aspengren, S., Skold, H. N., Quiroga, G., Martensson, L., Wallin, M. (2003). Noradrenaline- and melatonin-mediated regulation of pigment aggregation in fish melanophores. *Pigment Cell Res.* 16(1):59–64.
- Beinot, J. (1935). Stimulation par la lumière artificielle du développement testiculaire chez des canards aveugles per section du nerf optique. *CR Soc. Biol. (Paris)*. 120:133–136.
- Bellingham, J., Foster, R. G. (2002). Opsin and mammalian photoentrainment. *Cell Tissue Res.* 309(1):57–71.
- Bellingham, J., Whitmore, D., Philp, A. R., Wells, D. J., Foster, R. G. (2002). Zebrafish melanopsin: isolation, tissue localization and phylogenetic position. *Mol. Brain Res.* 107(2):128–136.
- Bertolucci, C., Wagner, G., Foa, A., Gwinner, E., Brandstätter, R. (2003). Photoperiod affects amplitude but not duration of in vitro melatonin production in the ruin lizard (*Podarcis sicula*). *J. Biol. Rhythms* 18:63–70.
- Bissinger, B. E. (1980). Role of the parietal eye in the homing behavior of lizards. *American Zoologist* 20:842.
- Blackshaw, S., Snyder, S. H. (1997). Parapinopsin, a novel catfish opsin localized to the parapineal organ, defines a new gene family. *J. Neurosci.* 17:8083–8092.
- Bolliet, V., Ali, M. A., Anctil, M., Zachmann, A. (1993). Melatonin secretion in vitro from the pineal complex of the lamprey *Petromyzon marinus*. *Gen. Comp. Endocrinol.* 89(1):101–106.
- Bolliet, V., Ali, M. A., Lapointe, F. J., Falcon, J. (1996). Rhythmic melatonin secretion in different teleost species: an in vitro study. *J. Comp. Physiol. B* 165(8):677–683.





- Brandstätter, R. (2003). Encoding time of day and time of year by the avian circadian system. *J. Neuroendocrinol.* 15(4):398–404.
- Brandstätter, R., Kumar, V., Van't Hof, T. J., Gwinner, E. (2000). Photoperiodic information acquired and stored in vivo is retained in vitro by a circadian oscillator, the avian pineal gland. *Proc. Natl. Acad. Sci. USA* 97(22):12324–12328.
- Cahill, G. (2002). Circadian organization in fish and Amphibians. In: Kumar, V., ed. *Biological Rhythms*. New Delhi: Narosa Publishing House, 120–128.
- Cole, W. C., Youson, J. H. (1981). The effect of pinealectomy, continuous light, and continuous darkness on metamorphosis of anadromous sea lampreys, *Petromyzon marinus* L. *J. Exp. Zool.* 218(3):397–404.
- Coon, S. L., Begay, V., Falcon, J., Klein, D. C. (1998). Expression of melatonin synthesis genes is controlled by a circadian clock in the pike pineal organ but not in the trout. *Biol. Cell* 90(5):399–405.
- Daniolos, A., Lerner, A. B., Lerner, M. R. (1990). Action of light on frog pigment cells in culture. *Pigment Cell Res.* 3(1):38–43.
- de Miguel, E., Rodicio, M. C., Anadon, R. (1990). Organization of the visual system in larval lampreys: an HRP study. *J. Comp. Neurol.* 302(3):529–542.
- Deutschlander, M. E., Borland, S. C., Phillips, J. B. (1999). Extraocular magnetic compass in newts. *Nature* 400(6742):324–325.
- Drivenes, O., Soviknes, A. M., Ebbesson, L. O., Fjose, A., Seo, H. C., Helvik, J. V. (2003). Isolation and characterization of two teleost melanopsin genes and their differential expression within the inner retina and brain. *J. Comp. Neurol.* 456(1):84–93.
- Ellis-Quinn, B. A., Simon, C. A. (1991). Lizard homing behavior: the role of the parietal eye during displacement and radio-tracking, and time-compensated celestial orientation in the lizard *Sceloporus jarrovi*. *Behav. Ecol. Sociobiol.* 28:397–407.
- Engbretson, A. (1992). Neurobiology of the lacertilian parietal eye system. *Ethol. Ecol. Evol.* 4:89–107.
- Foà, A. (1991). The role of the pineal and the retinae in the expression of circadian locomotor rhythmicity in the ruin lizard, *Podarcis sicula*. *J. Comp. Physiol. A* 169:201–207.
- Foà, A., Flamini, M., Innocenti, A., Minutini, L., Monteforti, G. (1993). The role of the extraretinal photoreception in the circadian system of the ruin lizards *Podarcis sicula*. *Comp. Bioch. Physiol.* 105A:223–230.
- Forsell, J., Holmqvist, B., Ekstrom, P. (2002). Molecular identification and developmental expression of UV and green opsin mRNAs in the pineal organ of the Atlantic halibut. *Dev. Brain Res.* 136(1):51–62.
- Foster, R. G., Follett, B. K. (1985). The involvement of a rhodopsin-like photopigment in the photoperiodic response of the japanese quail. *J. Comp. Physiol. A* 157:519–528.
- Foster, R. G., Hankins, M. W. (2002). Non-rod, noncone photoreception in the vertebrates. *Prog. Retin. Eye Res.* 21(6):507–527.
- Foster, R. G., Garcia-Fernandez, J. M., Provencio, I., De Grip, W.J. (1993). Opsin localization and chromophore retinoids identified within the basal brain of the lizard *Anolis carolinensis*. *J. Comp. Physiol. A* 172:33–45.





- Foster, R. G., Grace, M. S., Provencio, I., DeGrip, W. J., Garcia-Fernandez, J. M. (1994). Identification of vertebrate deep brain photoreceptors. *Neurosci. Biobehav. Rev.* 18:541–546.
- Fraenkel, G., Gunn, D. L. (1940). *The Orientation of Animals*. New York: Dove Publ.
- Freake, M. J. (2001). Homing behaviour in the sleepy lizard (*Tiliqua rugosa*): the role of cues and the parietal eye. *Behav. Ecol. Sociobiol.* 50(6):563–569.
- Gamse, J. T., Shen, Y. C., Thisse, C., Thisse, B., Raymond, P. A., Halpern, M. E., Liang, J. O. (2002). Otx5 regulates genes that show circadian expression in the zebrafish pineal complex. *Nat. Genet.* 30(1):117–121.
- Garcia-Fernandez, J. M., Jimenez, A. J., Gonzalez, B., Pombal, M. A., Foster, R. G. (1997). An immunocytochemical study of encephalic photoreceptors in three species of lamprey. *Cell Tissue Res.* 288(2):267–278.
- Garg, S. K., Sundararaj, B. I. (1986). Role of pineal in the regulation of some aspects of circadian rhythmicity in the catfish, *Heteropneustes fossilis* (Bloch). *Chronobiologia* 13(1):1–11.
- Grace, M. S., Alones, V., Menaker, M., Foster, R. G. (1996). Light perception in the vertebrate brain: an ultrastructural analysis of opsin- and vasoactive intestinal polypeptide-immunoreactive neurons in iguanid lizards. *J. Comp. Neurol.* 367:575–594.
- Green, C. B., Liang, M. Y., Steenhard, B. M., Besharse, J. C. (1999). Ontogeny of circadian and light regulation of melatonin release in *Xenopus laevis* embryos. *Dev. Brain Res.* 117(1):109–116.
- Guglielmotti, V., Vota-Pinardi, U., Fiorino, L., Sada, E. (1997). Seasonal variations in the frontal organ of the frog: structural evidence and physiological correlates. *Comp. Biochem. Physiol. A* 116(2):137–141.
- Gundy, G. C., Ralph, C. L., Wurst, G. Z. (1975). Parietal eyes in lizards: zoogeographical correlates. *Science* 190(4215):671–673.
- Gwinner, E., Brandstatter, R. (2001). Complex bird clocks. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356(1415):1801–1810.
- Harada, Y., Goto, M., Ebihara, S., Fujisawa, H., Kegasawa, K., Oishi, T. (1998). Circadian locomotor activity rhythms in the African clawed frog, *Xenopus laevis*: the role of the eye and the hypothalamus. *Biol. Rhythm Res.* 29(1):30–48.
- Innocenti, A., Minutini, L., Foà, A. (1993). The pineal and circadian rhythms of temperature selection and locomotion in lizards. *Physiol. Behav.* 53(5):911–915.
- Jamieson, D., Roberts, A. (2000). Responses of young *Xenopus laevis* tadpoles to light dimming: possible roles for the pineal eye. *J. Exp. Biol.* 203(12):1857–1867.
- Joss, J. M. (1973a). The pineal complex, melatonin, and colour change in the lamprey *Lampetra fluviatilis*. *Gen. Comp. Endocrinol.* 21(1):188–195.
- Joss, J. M. (1973b). Pineal-gonad relationships in the lamprey *Lampetra fluviatilis*. *Gen. Comp. Endocrinol.* 21(1):118–122.
- Justis, C. S., Taylor, D. H. (1976). Extraocular photoreception and compass orientation in larval bullfrogs, *Rana catesbeiana*. *Copeia*. 1976:98–105.
- Kawamura, S., Yokoyama, S. (1996). Molecular characterization of the pigeon *P*-opsin gene. *Gene* 182(1–2):213–214.



- Kawamura, S., Yokoyama, S. (1997). Expression of visual and nonvisual opsins in American chameleon. *Vision Res.* 37:1867–1871.
- Kojima, D., Mano, H., Fukada, Y. (2000). Vertebrate ancient long opsin: a green-sensitive photoreceptive molecule present in zebrafish deep brain and retinal horizontal cells. *J. Neurosci.* 20:2845–2851.
- Korf, H. W., Schomerus, C., Stehle, J. H. (1998). The pineal organ, its hormone melatonin, and the photoneuroendocrine system. *Adv. Anat. Embryol. Cell Biol.* 146:1–100.
- 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 Lett.* 506(1):69–72.
- Mano, H., Kojima, D., Fukada, Y. (1999). Exo-rhodopsin: a novel rhodopsin expressed in the zebrafish pineal gland. *Mol. Brain Res.* 73(1–2):110–108.
- Masuda, T., Iigo, M., Mizusawa, K., Aida, K. (2003). Retina-type rhodopsin gene expressed in the brain of a teleost, ayu (*Plecoglossus altivelis*). *Zoolog. Sci.* 20(8):989–997.
- Masuda, H., Oishi, T., Ohtani, M., Michinomae, M., Fukada, Y., Shichida, Y., Yoshizawa, T. (1994). Visual pigments in the pineal complex of the Japanese quail, Japanese grass lizard and bullfrog: immunocytochemistry and HPLC analysis. *Tissue Cell* 26(1):101–113.
- Max, M., Menaker, M. (1992). Regulation of melatonin production by light, darkness, and temperature in the trout pineal. *J. Comp. Physiol. A* 170(4):479–489.
- Menaker, M. (1968). Extraretinal light perception in the sparrow. I. Entrainment of the biological clock. *Proc. Natl. Acad. Sci. USA* 59(2):414–421.
- Menaker, M. (1972). Nonvisual light reception. *Sci. Am.* 226(3):22–29.
- Menaker, M. (1985). Eyes—the second (and third) pineal glands? *Ciba Found. Symp.* 117:78–92.
- Menaker, M., Keatts, H. (1968). Extraretinal light perception in the sparrow. II. Photoperiodic stimulation of testis growth. *Proc. Natl. Acad. Sci. USA* 60(1):146–151.
- Menaker, M., Wisner, S. (1983). Temperature-compensated circadian clock in the pineal of *Anolis*. *Proc. Natl. Acad. Sci. USA* 80:6119–6121.
- Miller, W. H., Wolbarsht, M. L. (1962). Neural activity in the parietal eye of lizard. *Science* 35:316–317.
- Minamoto, T., Shimizu, I. (2002). A novel isoform of vertebrate ancient opsin in a smelt fish, *Plecoglossus altivelis*. *Biochem. Biophys. Res. Commun.* 290(1):280–286.
- Minutini, L., Innocenti, A., Bertolucci, C., Foà, A. (1995). Circadian organization in the ruin lizard *Podarcis sicula*: the role of the suprachiasmatic nuclei of the hypothalamus. *J. Comp. Physiol. A* 176:281–288.
- Morita, Y., Tabata, M., Uchida, K., Samejima, M. (1992). Pineal-dependent locomotor activity of lamprey, *Lampetra japonica*, measured in relation to LD cycle and circadian rhythmicity. *J. Comp. Physiol. A* 171:555–562.
- Moutsaki, P., Bellingham, J., Soni, B. G., David-Gray, Z. K., Foster, R. G. (2000). Sequence, genomic structure and tissue expression of carp (*Cyprinus carpio* L.) vertebrate ancient (VA) opsin. *FEBS Lett.* 473(3):316–322.



- Moutsaki, P., Whitmore, D., Bellingham, J., Sakamoto, K., David-Gray, Z. K., Foster, R. G. (2003). Teleost multiple tissue (tmt) opsin: a candidate photopigment regulating the peripheral clocks of zebrafish? *Mol. Brain Res.* 112(1–2):135–145.
- Okano, T., Yoshizawa, T., Fukada, Y. (1994). Pinopsin is a chicken pineal photoreceptive molecule. *Nature* 372:94–97.
- Okano, K., Okano, T., Yoshikawa, T., Masuda, A., Fukada, Y., Oishi, T. (2000). Diversity of opsin immunoreactivities in the extraretinal tissues of four anuran amphibians. *J. Exp. Zool.* 286(2):136–142.
- Okano, T., Takanaka, Y., Nakamura, A., Hirunagi, K., Adachi, A., Ebihara, S., Fukada, Y. (1997). Immunocytochemical identification of pinopsin in pineal glands of chicken and pigeon. *Mol. Brain Res.* 50(1–2):190–196.
- Pasqualetti, M., Bertolucci, C., Ori, M., Innocenti, A., Magnone, M. C., De Grip, W. J., Nardi, I., Foà, A. (2003). Identification of circadian brain photoreceptors mediating photic entrainment of behavioural rhythms in lizards. *Eur. J. Neurosci.* 18(2):364–372.
- Phillips, J. B., Deutschlander, M. E., Freake, M. J., Borland, S. C. (2001). The role of extraocular photoreceptors in newt magnetic compass orientation: parallels between light-dependent magnetoreception and polarized light detection in vertebrates. *J. Exp. Biol.* 204(14):2543–2552.
- Philp, A. R., Bellingham, J., Garcia-Fernandez, J., Foster, R. G. (2000a). A novel rod-like opsin isolated from the extra-retinal photoreceptors of teleost fish. *FEBS Lett.* 468(2–3):181–188.
- Philp, A. R., Garcia-Fernandez, J. M., Soni, B. G., Lucas, R. J., Bellingham, J., Foster, R. G. (2000b). Vertebrate ancient (VA) opsin and extraretinal photoreception in the Atlantic salmon (*Salmo salar*). *J. Exp. Biol.* 203:1925–1936.
- Provencio, I., Jhang, G., DeGrip, W. J., Hayes, W. P., Rollag, M. D. (1998). Melanopsin: an opsin in melanophores, brain and eye. *Proc. Natl. Acad. Sci. USA* 95:340–345.
- Quay, W. B. (1979). The parietal eye-pineal complex. In: Glans, C., Northcutt, R. G., Ulinski, P., eds. *Biology of the Reptilia*. New York: Academic Press, 245–406.
- Roenneberg, T., Foster, R. G. (1997). Twilight times: light and the circadian system. *Photochem. Photobiol.* 66:549–561.
- Roth, J. J., Gern, W. A., Roth, E. C., Ralph, C. L., Jacobson, E. (1980). Nonpineal melatonin in the alligator (*Alligator mississippiensis*). *Science* 210(4469):548–550.
- Scharrer, E. (1928). Die Lichtempfindlichkeit blinder Elritzen. I. Untersuchungen über das Zwischenhirn der Fische. *Z. Vergl. Physiol.* 7:1–38.
- Shand, J., Foster, R. G. (1999). The extraretinal photoreceptors of nonmammalian vertebrates. In: Archer, S., Djamgoz, J., Loew, E., eds. *Adaptive Mechanisms in the Ecology of Vision*. Dordrecht, Boston, London: Kluwer Academic Publishers, 197–222.
- Silver, R., Witkovsky, P., Horvath, P., Alones, V., Barnstable, C. J., Lehman, M. N. (1988). Coexpression of opsin- and VIP-like-immunoreactivity in CSF-contacting neurons of the avian brain. *Cell Tissue Res.* 253:189–198.
- Sinsch, U. (1990). Migration and orientation in anuran amphibians. *Ethol. Ecol. Evol.* 2:65–79.



- Solessio, E., Engbretson, G. A. (1993). Antagonistic chromatic mechanisms in photoreceptors of the parietal eye of lizards. *Nature* 364(6436):442–445.
- Solessio, E., Engbretson, G. A. (1999). Electroretinogram of the parietal eye of lizards: photoreceptor, glial, and lens cell contributions. *Vis. Neurosci.* 16(5):895–907.
- Taniguchi, Y., Hisatomi, O., Yoshida, M., Tokunaga, F. (2001). Pinopsin expressed in the retinal photoreceptors of a diurnal gecko. *FEBS Lett.* 496(2–3):69–74.
- Taniguchi, M., Murakami, N., Nakamura, H., Nasu, T., Shinohara, S., Etoh, T. (1993). Melatonin release from pineal cells of diurnal and nocturnal birds. *Brain Res.* 620(2):297–300.
- Taylor, D. H., Adler, K. (1973). Spatial orientation by Salamanders using plane-polarized light. *Science* 181(96):285–287.
- Taylor, D. H., Adler, K. (1978). The pineal body: site of extraocular perception of celestial cues for orientation in the tiger salamander (*Ambystoma tigrinum*). *J. Comp. Physiol. A* 124:357–361.
- Taylor, D. H., Ferguson, D. E. (1970). Extraoptic celestial orientation in the southern cricket frog *Acris gryllus*. *Science* 168(929):390–392.
- Tosini, G., Menaker, M. (1996). The pineal complex and melatonin affects the daily rhythm of temperature selection in the green iguana. *J. Comp. Physiol. A* 179:135–142.
- Tosini, G., Menaker, M. (1998). Multioscillatory circadian organization in a vertebrate, *Iguana iguana*. *J. Neurosci.* 18(3):1105–1114.
- Tosini, G., Bertolucci, C., Foà, A. (2001). The circadian system of reptiles: a true multioscillatory and multiphotoreceptive system. *Physiol. Behav.* 72:461–471.
- Underwood, H. (1973). Retinal and extraretinal photoreceptor mediate entrainment of the circadian locomotor rhythms in lizard. *J. Comp. Physiol.* 83:187–222.
- Underwood, H. (1983). Circadian organization in the lizard *Anolis carolinensis*: a multioscillator system. *J. Comp. Physiol.* 152:265–274.
- Underwood, H. (1990). The pineal and melatonin: regulators of circadian function in lower vertebrates. *Experientia* 46:120–128.
- Underwood, H., Groos, G. (1982). Vertebrate circadian rhythms: retinal and extraretinal photoreception. *Experientia* 38:1013–1021.
- Underwood, H., Menaker, M. (1976). Extraretinal photoreception in lizard. *Photochem. Photobiol.* 24:277–241.
- Vigh, B., Manzano, M. J., Zadori, A., Frank, C. L., Lukats, A., Rohlich, P., Szel, A., David, C. (2002). Nonvisual photoreceptors of the deep brain, pineal organs and retina. *Histol. Histopathol.* 17(2):555–590.
- Vigh-Teichmann, I., Vigh, B., Olsson, R., van Veen, T. (1984). Opsin-immunoreactive outer segments of photoreceptors in the eye and in the lumen of the optic nerve of the hagfish, *Myxine glutinosa*. *Cell Tissue Res.* 238(3):515–522.
- Vollrath, L. (1981). The Pineal Organ. In: Oksche, A., Vollrath, L., eds. *Hanbuch der mikroskopischen Anatomie des Menschen, VI/7*. Berlin, Heidelberg, New York: Springer.
- von Frisch, K. (1911). Beitrage zur Physiologie der Pigmentzellen inder Fischhaut. *Pflügers Arch.* 138:319–387.





### Circadian Photoreception

519

- Wada, Y., Okano, T., Adachi, A., Ebihara, S., Fukada, Y. (1998). Identification of rhodopsin in the pigeon deep brain. *FEBS Lett.* 424:53–56.
- Xiong, W. H., Solessio, E. C., Yau, K. W. (1998). An unusual cGMP pathway underlying depolarizing light response of the vertebrate parietal-eye photoreceptor. *Nat. Neurosci.* 1(5):359–365.

