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Review

Nonvisual photoreceptors of the deep brain, pineal organs and retina

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Summary. The role of the nonvisual photoreception is to synchronise periodic functions of living organisms to the environmental light periods in order to help survival of various species in different biotopes. In vertebrates, the so-called deep brain (septal and hypothalamic) photoreceptors, the pineal organs (pineal- and parapineal organs, frontal- and parietal eye) and the retina (of the "lateral" eye) are involved in the light-based entrain of endogenous circadian clocks present in various organs. In humans, photoperiodicity was studied in connection with sleep disturbances in shift work, seasonal depression, and in jet-lag of transmeridional travellers. In the present review, experimental and molecular aspects are discussed, focusing on the histological and histochemical basis of the function of nonvisual photoreceptors. We also offer a view about functional changes of these photoreceptors during pre- and postnatal development as well as about its possible evolution. Our scope in some points is different from the generally accepted views on the nonvisual photoreceptive systems.

The *deep brain photoreceptors* are hypothalamic and septal nuclei of the periventricular cerebrospinal fluid (CSF)-contacting neuronal system. Already present in the lancelet and representing the most ancient type of vertebrate nerve cells ("protoneurons"), CSF-contacting neurons are sensory-type cells sitting in the wall of the brain ventricles that send a ciliated dendritic process into the CSF. Various opsins and other members of the phototransduction cascade have been demonstrated in telencephalic and hypothalamic groups of these neurons. In all species examined so far, deep brain photoreceptors play a role in the circadian and circannual regulation of periodic functions.

Mainly called pineal "glands" in the last decades, the *pineal organs* actually represent a differentiated form of encephalic photoreceptors. Supposed to be intra- and extracranially outgrown groups of deep brain photoreceptors, pineal organs also contain neurons and glial elements. Extracranial pineal organs of submammalians are cone-dominated photoreceptors sensitive to different wavelengths of light, while intracranial pineal organs predominantly contain rod-like photoreceptor cells and thus scotopic light receptors. Vitamin B-based light-sensitive cryptochromes localized immunocytochemically in some pineal cells may take part in both the photoreception and the pacemaker function of the pineal organ.

In spite of expressing phototransduction cascade molecules and forming outer segment-like cilia in some species, the mammalian pineal is considered by most of the authors as a light-insensitive organ. Expression of phototransduction cascade molecules, predominantly in young animals, is a photoreceptor-like characteristic of pinealocytes in higher vertebrates that may contribute to a light-percepting task in the perinatal entrainment of rhythmic functions. In adult mammals, adrenergic nerves - mediating daily fluctuation of sympathetic activity rather than retinal light information as generally supposed - may sustain circadian periodicity already entrained by light perinatally. Altogether three phases were supposed to exist in pineal entrainment of internal pacemakers: an embryological synchronization by light and in viviparous vertebrates by maternal effects (1); a light-based, postnatal entrainment (2); and in adults, a maintenance of periodicity by daily sympathetic rhythm of the hypothalamus.

In addition to its visual function, the lateral eye retina performs a nonvisual task. Nonvisual retinal light perception primarily entrains genetically-determined periodicity, such as rod-cone dominance, EEG rhythms or retinomotor movements. It also influences the suprachiasmatic nucleus, the primary pacemaker of the brain. As neither rods nor cones seem to represent the nonvisual retinal photoreceptors, the presence of additional photoreceptors has been supposed. Cryptochrome 1, a photosensitive molecule identified in retinal nerve cells and in a subpopulation of retinal photoreceptors, is a good candidate for the nonvisual

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photoreceptor molecule as well as for a member of pacemaker molecules in the retina.

When comparing various visual and nonvisual photoreceptors, transitory, "semivisual" (directional) light-perceptive cells can be detected among them, such as those in the parietal eye of reptiles. Measuring diffuse light intensity of the environment, semivisual photoreceptors also possess some directional light perceptive capacity aided by complementary lens-like structures, and screening pigment cells. Semivisual photoreception in aquatic animals may serve for identifying environmental areas of suitable illumination, or in poikilotermic terrestrial species for measuring direct solar irradiation for thermoregulation. As directional photoreceptors were identified among nonvisual light perceptive cells in the lancelet, but eyes are lacking, an early appearance of semivisual function, prior to a visual one (nonvisual → semivisual → visual?) in the vertebrate evolution was supposed.

Key words: Photoreceptor ultrastructure, Opsin immunocytochemistry, Phototransduction cascade, Efferent of terminal photoreceptors, Photoperiods

Introduction

In contrast to several body areas including skin, retinal pigment epithelium, iris, or chromatophores known to show *light sensitivity*, specialized *photoreceptor cell*s are only present in the lateral eye retina (to avoid confusion with pineal eyes, we use the expression "lateral eye"), in the pineal organs and in the so-called deep brain (septal and hypothalamic) photoreceptor areas of vertebrates. These photoreceptor cells may have visual, locator-type functions, as in the lateral eye, or *nonvisua*l, photodensitometer-type light perception, like the pineal organs and deep brain photoreceptors. Besides their visual, image-decoding function, the lateral eyes also have a nonvisual, photoperiodic light-perceptive function.

The earliest evidence for the existence of "deep encephalic photoreceptors" was provided in the first half of the last century. Young (1935) described that blinded and pinealectomised larval lampreys react to illumination of the head, a result that may be explained by the presence of some photosensitive brain areas. Benoit and Ott (1944) reported that illumination of the hypothalamus resulted in testicular growth of blind ducks. Recent studies show that deep brain photoreceptors are represented by the so-called cerebrospinal fluid (CSF)-contacting neurons of some septal and anterior hypotahalamic nuclei (Foster et al., 1994; Garcia-Fernandez and Foster, 1994; Grace et al., 1996; Garcia-Fernandez et al., 1997; Wada et al., 1998, 2000; Vígh et al., 2001).

The main task of both the nonvisual and semivisual photoreceptors is to inform the organism of the ambient light conditions. These receptors regulate the endogenous circadian and circannual timekeeping system and by this, influence seasonal functions like breeding, migration, moulting or colour change, and in humans, among others, circadian sleep- and seasonal affective-periodicity. The endogenous circadian rhythm of several organs also persists in constant light conditions with a period being nearly, but not exactly, 24 h. Environmental stimuli - first of all light - adjusts this endogenous circadian clock to astrologic periods. The suprachiasmatic nucleus of the hypothalamus has been shown to be the primary pacemaker of the brain that drives physiological and behavioral rhythms. Besides the suprachiasmatic master pacemaker, there are "slave" oscillators in several other organs including the retina and pineal organs. Photic information from the retina is conveyed to the suprachiasmatic nucleus by the retinohypothalamic tract and, indirectly, by the geniculohypothalamic tract (Illnerova et al., 2000; Moore et al., 2000; Shanan and Czeisler, 2000).

The pineal organ of higher vertebrates phylogenetically develops from two epithalamic eyes, the "third" and the "fourth eye" of the supposed four-

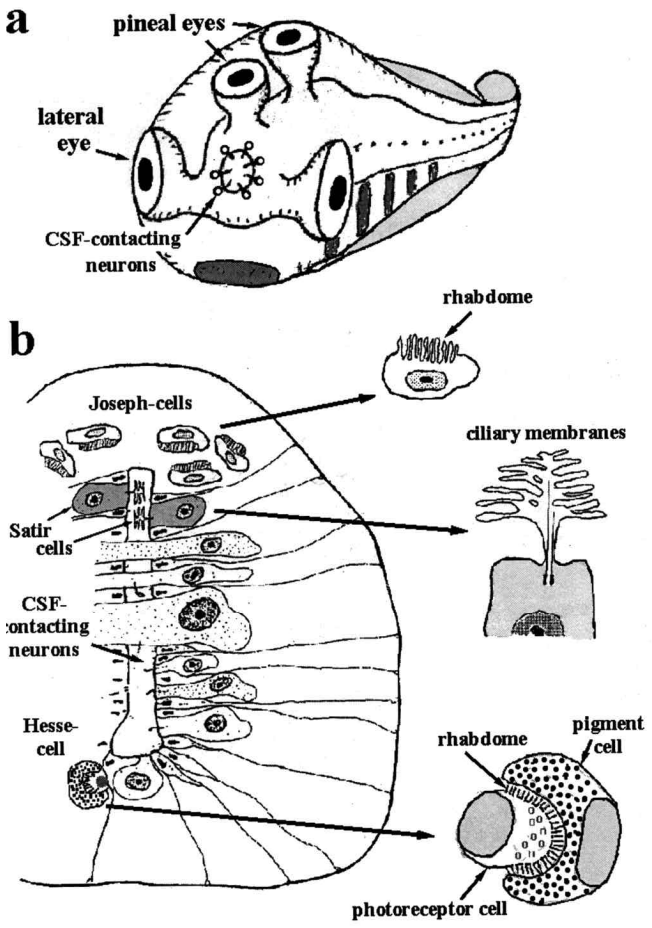

Fig. 1. a. Scheme on the hypothetic four-eyed protovertebrate. **b.** Scheme on the photoreceptor cells of the lancelet brain.

eyed protovertebrate (Fig. 1a). Correspondingly, in the cyclostome lamprey, representing one of the most simple recent craniate vertebrates, and in bony fishes two pineal organs are present: the pineal and parapineal organ. Besides the pineal organ, frogs have a frontal eye and some reptiles possess a parietal eye (Vigh and Vígh-Teichmann, 1988, 1989b, 1992b, 1999).

Electrophysiological recordings proved direct pineal photosensitivity in submammalians (Dodt and Meissl, 1982; Morita et al., 1991b; Meissl and Brandstätter, 1992). Photopigments were first shown to exist in the pineal of fish and frogs by microspectrophotometric recordings (Hartwig and Baumann, 1974). Opsins were first localized immunocytochemically in photoreceptor outer segments of the pineal complex of various fish and amphibian species, later in other vertebrates including mammals and human (Vígh-Teichmann et al., 1980b, 1993; Vígh and Vígh-Teichmann, 1981, 1988; Korf et al., 1985).

Several publications have summarised results about the functioning of individual members of the nonvisual photoreceptors. In the present review, we compare data (of about 500 papers) on the deep brain, pineal and retinal nonvisual photoreceptors, emphasizing the histological and hisochemical basis of their functions. Our scope may be different in some points from the general view on photoperiodic receptors. We also suggest a hypothesis on the pre- and postnatal changes in the role of the nonvisual photoreceptor system, as well as on its possible phylogenetic origin. In the first chapter we provide data on deep encephalic photoreceptors.

Deep brain photoreceptors

Since the pioneer works of von Frisch (1911), Scharrer (1928, 1964), Benoit (1935) and Young (1935), many studies pointed out the possible role of deep encephalic photoreceptors in mediating photoperiodism (Benoit and Ott, 1944; Oishi and Kato, 1968; Homma and Sakakibara, 1971; Oliver and Bayle, 1976, Homma et al., 1977; Oliver et al., 1977; Yokoyama et al., 1978). As already mentioned, later experiments suggested that some CSF-contacting neurons of the *hypothalamus* and *septum* may represent the photoreceptors involved in photoperiodism (Sicard et al., 1983; Follett et al., 1985; Foster et al., 1984, 1985, 1987; Kuenzel, 1993; Oishi and Ohashi, 1993; Yoshikawa et al., 1994; Kawamura and Yokoyama, 1997; Wada et al., 1998; Yoshikawa et al., 1998; Blackshaw and Snyder, 1999; Kojima and Fukada, 1999; Kojima et al., 2000a,b). To have some insight into the evolution of nonvisual photoreceptors, we first discuss the encephalic photoreceptors of the lancelet and lower vertebrates.

The **acranian lancelet** (*Branchiostoma lanceolatum*) represents recent chordates having a nervous system similar but less differentiated than that of vertebrates. There are no lateral eyes in this species, but in addition to the so-called Satir cells that sit on the upper part of the brain vesicle, there are numerous photoreceptors in the central nervous system (Fig 1b). In the dorsal portion of the brain and the rostral ventral spinal cord, three types of photoreceptor cells were found: Joseph cells and Hesse cells, both supplied with a rhabdome composed by microvilli, further, Satir cells displaying ciliary photoreceptor lamellae, thus being similar to light-sensitive cells of vertebrates. All neurons of the brain and spinal cord are of the CSF-contacting type, regarded as "protoneurons" in the vertebrate line of evolution. Some of them may also represent light-sensitive cells (Eakin and Westfall, 1962; Vígh-Teichmann and Vígh, 1974; Ruiz and Anadon, 1991a,b; Vígh and Vígh-Teichmann, 1982, 1998, 1999).

Rhabdome-forming cells are the main photoreceptors in invertebrates. The rhabdomeric Hesse cells of the lancelet spinal cord are associated with shadowing pigment cells. These pigment cells filled by dark pigment granules enclose the rhabdomic microvilli like a cup and the light can only enter the cup from one side. This organisation enables a directional photoreception, that is thought to be a transitory function between nonvisual and visual light perception. Hesse cells are sitting in various segments of the spinal cord, and the open side of the sensory-cell/pigment-cell complex looks in different directions, thus enabling a differential perception of light as a function of the direction of the incoming light. Photoreception may serve negative phototropic behaviour in the larval lancelet, as shown by their staying near the bottom of the seashore during daytime, and coming up to the surface only at night (Eakin, 1968, Vígh-Teichmann and Vígh, 1983; Watanabe and Yoshida, 1986; Ruiz and Anadon, 1991a; Vígh and Vígh-Teichmann, 1999; Northcutt, 2001).

A seasonal nervous regulation of the release of gonadotropin was postulated in connection with Hatschek's pit, a possible homologue of the anterior pituitary of vertebrates (Gorbman et al., 1999; Massari et al., 1999). The functional and evolutionary significance of the rhabdomeric and ciliary photoreceptors in relation to the ciliary photoreceptors of other chordates was discussed by Ruiz and Anadon (1991a,b).

Cyclostomes are the most simple craniate vertebrates possessing all main brain parts similar to those of higher vertebrates. The hagfish (*Myxine glutinosa*) lacks the pineal organ, and the lateral eyes are rudimentary. Extraretinally, opsin immunoreactive cells has been found in the hagfish optic nerve around multiple tubular lumina. No opsin immunoreactivity was found elsewhere in serial sections of the entire brain (Vígh-Teichmann et al., 1984).

In the *lamprey* (*Petromyzon marinus*, *Lampetra fluviatilis*, *Ichthyomyson unicuspis*) diencephalic neuronal areas were proposed to contain deep brain photoreceptors on the basis of the presence of immunoreactive rod and cone opsins, alpha-transducin and arrestin. The labelled neurons proved to be CSF-contacting neurons of the preoptic nucleus (Fig. 2a,b), the postoptic commissural nucleus, as well as of the

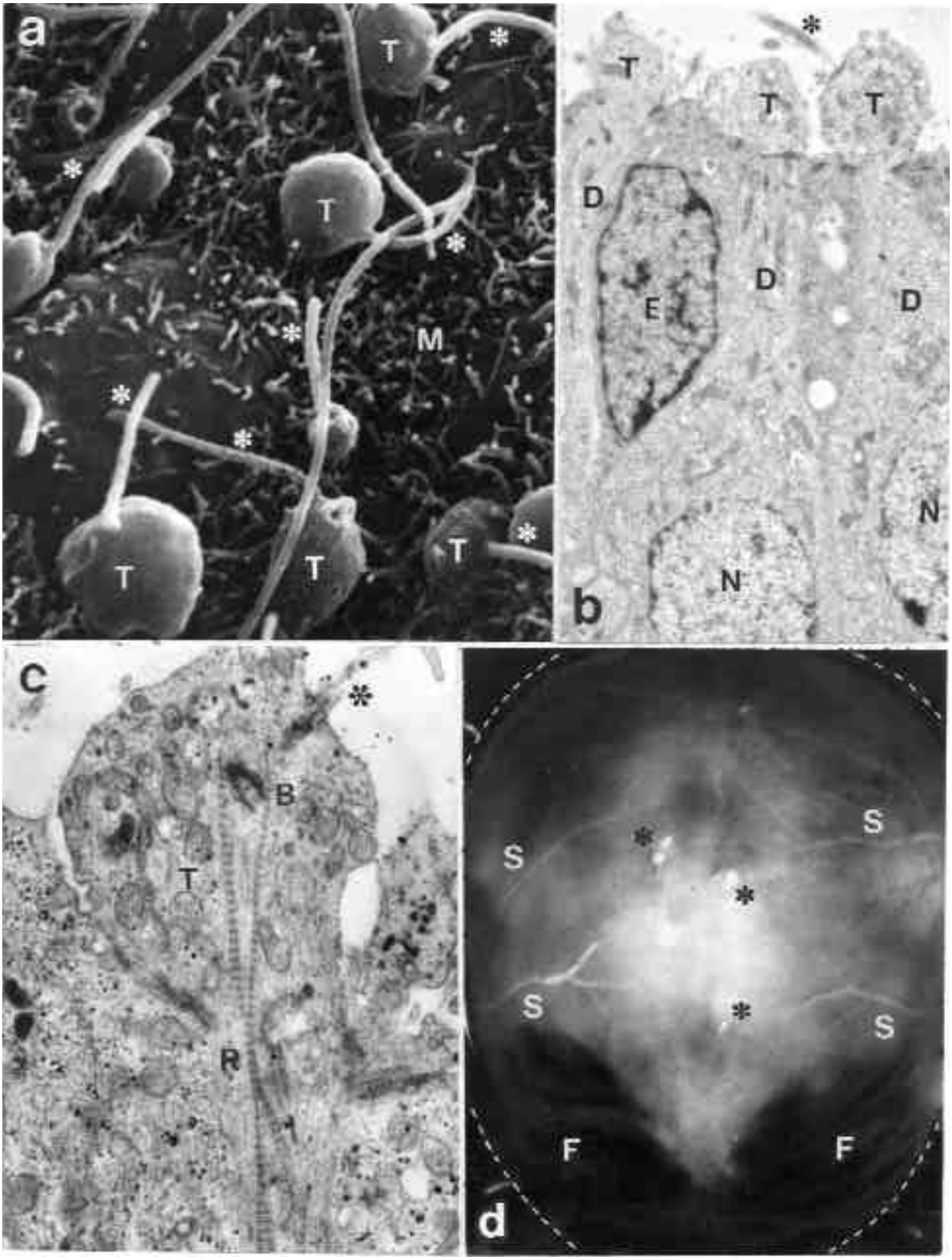

Fig. 2. a. Scanning electron microscopic view of intraventricular ciliated dendrite terminals (T) of CSF-contacting neurons in the lamprey. Asterisk: sensory cilia, M: ependymal microvilli. x 14,000. **b.** Fine structure of the preoptic CSF-contacting neurons of the lamprey. Asterisk: cilium; D: denrites; N: nucleus; E: ependymal cell; T: CSF-contacting terminal. x 12,500. **c.** Intraventricular dendrite terminal (T) of the preoptic CSF-contacting neuron of *Triturus cristatus*. B: basal body; asterisk: cilium; R: rootlet fiber. x 19,500. **d.** Light (100 W. lamp) penetrates the human skull (contour dotted). F: hyperostosis frontalis interna; S: sulcus of the medial meningeal artery; asterisk: foveolae granulares. x 0.65

ventral and dorsal hypothalamic nuclei. Some labelled neurons in the epithalamus and caudal hypothalamus were found to be devoid of direct contact with the ventricular lumen (Foster et al., 1994; Garcia-Fernandez et al., 1997).

Antibodies raised against various visual opsins, and the C terminal of the α-subunit of retinal G protein (transducin) labelled CSF-contacting neurons of the postoptic commissural nucleus and ventral thalamic nucleus in the larval lamprey (*Petromyzon marinus*) (Garcia-Fernandez and Foster, 1994). It was supposed that in the lamprey brain, representing an ancestral form of the vertebrate central nervous system, the different populations of encephalic photoreceptors are directly associated with discrete brain centers involved in various behavioural and physiological responses.

Concerning **fishes**, Soni and Foster (1997) have isolated a novel opsin gene from the eyes of Atlantic salmon. Based on the cDNA sequence, the presence of an opsin-like protein different from other known opsin families has been predicted. Phylogenetic analysis suggests that this opsin belongs to an ancient, earlier not recognized photopigment family of vertebrates termed VA (vertebrate ancient) opsin (Kojima et al., 1997, 1998). VA opsin was detected in the suprachiasmatic nucleus, parvocellular and magnocellular preoptic nucleus of Atlantic salmon and carp (Soni and Foster, 1997; Moutsaki et al., 2000; Philp et al., 2000a,b). The presence of opsin in the suprachiasmatic nucleus of fishes suggests that the suprachiasmatic pacemaker of higher vertebrates may have originated from deep encephalic photoreceptors of lower vertebrates.

VAL-opsin (VA-long), a novel variant of VA opsin, representing a green-sensitive (λ_{max} approximately 500 nm) photoreceptive molecule, was demonstrated in the deep brain of zebrafish (Kojima et al., 2000a). Antibodies specific for the C-terminal of VAL opsin labelled neurons around the third ventricle at the level of the central thalamus. The most intense reaction was observed in CSF-contacting-like cells distributed in a 200 µm long area at the central posterior thalamic nucleus. Nearly the same brain region of the minnow was proposed by von Frisch (1911) to play a role in regulation of skin colour. Since the skin of zebrafish becomes pale in the dark and darkens upon light exposure, Kojima and coworkers (2000a,b) suggested a role for the VAL opsin-containing deep encephalic photoreceptors in the skin colour regulation depending on environmental light conditions. A role for encephalic photoreceptors in the swimming and feeding reflexes of the European minnow was also demonstrated earlier (Scharrer, 1928).

In **amphibians**, urodeles and anurans have similar CSF-contacting neuronal nuclei in the diencephalon (Fig. 2c). In *Rana esculenta* and *R. ridibunda*, electrical responses have been demonstrated to light in diencephalic nuclei and mesencephalic tectal areas of blinded and pinealectomised frogs (Cadusseau and Galand, 1981).

Deep encephalic photoreceptors have first been localised in the toad *(Bufo japonicu*s) and in the bullfrog (*Rana catesbeiana*) by Yoshikawa and coworkers (1994). Immunoreactivity with antibodies against bovine rhodopsin, rod- and cone transducin was detected in the hypothalamic CSF-contacting neurons of the preoptic and suprachiasmatic nucleus in the bullfrog. Antibodies against toad retinal rhodopsin reacted with CSF-contacting neurons of the septal, and preoptic (anterior and magnocellular) nucleus (Okano et al., 2000). Pinopsin has also been identified in the anterior preoptic nucleus of the toad (Kojima and Fukada, 1999). Using HPLC analysis, Masuda and coworkers (1994) detected 11-cis and all-trans retinal in the ventral part of the bullfrog diencephalon including the hypothalamus.

In *Bufo japonicus* a cDNA clone encoding a deep brain photoreceptive molecule from the hypothalamic cDNA library has been isolated. The deduced amino acid sequence showed a 75-76% similarity to chicken pinopsin. Antibodies raised against the C-terminal of this toad pineal opsin (pinopsin) stained CSF-contacting neurons in the anterior preoptic nucleus (Yoshikawa et al., 1998).

In addition to the opsins already mentioned, the gene of melanopsin, the opsin of photosensitive dermal melanophores of *Xenopus laevis* was found to be transcribed in Xenopus tadpoles (stages 56 and 57) in the ventral part of the magnocellular preoptic nucleus and in the suprachiasmatic nucleus. These results suggest a nonvisual photoreceptive role of these neurons in the photic control of skin pigmentation or circadian and circannual photoperiodic physiology (Provencio et al., 1998).

In **reptiles**, deep brain photoreceptors have been found to mediate circadian entrainment of locomotor activity after blinding and removal of the pineal complex (pineal and parietal organ) of lizards (Underwood and Menaker, 1976). Similarly, encephalic photoreceptors were suggested to entrain and control circadian activity of American alligator, which does not have pineal organs (Roth et al., 1977; Kavaliers, 1980; Kavaliers and Ralph, 1981).

Deep encephalic photoreceptors were first localized by biochemical and immunohistochemical methods in iguanid lizards. Specific retinoids associated with phototransduction (11-cis and all-trans-3,4-didehydroretinaldehyde) were identified within anterior brain extracts of the lizards (Foster et al., 1993, 1994).

In *Anolis carolinensis* and *Iguana iguana*, CSF-contacting bipolar neurons were immunolabelled in the lateral septum, with monoclonal antibody COS-1 recognizing long-wavelength-sensitive pigments of chicken and mammalian cones (Szél et al., 1986, 1988; Röhlich and Szél, 1993) and with CERN-874, -906 antibodies generated against chicken retinal cone opsins (Foster et al., 1993). CSF-contacting neurons remained negative using other antisera (OS-2, recognizing rod and cone visual pigments, rod-specific CERN-JS858, bovine opsin and an other chicken cone-opsin antibody). These

bipolar neurons situated in the ependymal layer of the basal region of the lateral ventricle, send ciliated dendrite terminals to the CSF, and the cytoplasm contains numerous large electron-dense vesicles. Multiple synaptic contacts have been found on the soma and dendritic processes (Grace et al., 1993; Hirunagi et al., 1993; Foster et al., 1994).

The CSF-contacting neurons of the reptilian lateral septum also bind VIP (vasoactive intestinal peptide) antibodies (Grace et al., 1993, 1996; Hirunagi et al., 1993). VIP immunoreactive CSF-contacting neurons were found in the lateral septum of several other reptiles as well (Rommel, 1987; Petko and Ihinovien, 1989). The lateral division of the septum mediates descending limbic cortical pathways to diencephalic areas (Jakab and Léránth, 1995), whereas the VIP immunoreactive CSF-contacting neurons may influence these limbic-diencephalic afferentations.

Early experimental works in **birds** showed, that testicular growth in blind ducks can be induced by illuminating the hypothalamus (Benoit, 1935; Benoit and Ott, 1944). Similar results have been obtained in the house sparrow (Menaker, 1968, 1972; Menaker and Keatts, 1968; Menaker et al., 1970), in the white crowned sparrow (Yokojama et al., 1978), and in the quail (Oliver et al., 1977). Further, expression of migratory behaviour was induced by illumination of the basal hypothalamus (Yokoyama and Farner, 1978). A maximum spectral sensitivity around 492 nm indicating the presence of a rhodopsin-like photopigment has been reported for the photoperiodic response of the Japanese quail (Foster and Follet,1985; Foster et al., 1985).

In addition to preoptic-suprachiasmatic regions of the hypothalamus, light-sensitive sites were also localized to septal brain areas within the parolfactory lobe (Homma and Sakakibara, 1971; Oliver and Bayle, 1976, 1982; Glass and Lauber, 1981; Kuenzel, 1993). Opsin- and VIP-immunoreactive CSF-contacting neurons have first been identified along the lateral ventricle in the lateral septum and in the hypothalamus of the quail, *Coturnix coturnix*, duck, *Anas platyrhynchos*, and ring dove, *Streptopelia risoria* (Silver et al., 1988). Similar results were published on deep brain CSF-contacting neurons of birds by Foster and coworkers (1994). VIP-immunoreactive CSF-contacting neurons of the lateral septum were found to form a circumventricular organ-like, circumscribed area ("lateral septal organ") in the duck (Hirunagi et al., 1995).

Rhodopsin gene expression was detected in the pigeon lateral septum. The nucleotide sequence of these deep brain rhodopsin cDNA clones corresponded with that of the retinal one. Immunoreactive rhodopsin and alpha-subunit of rod-type transducin were colocalized in CSF-contacting neurons of the pigeon lateral septum. In the same area, RT-PCR analyses showed gene expression of rod/cone phototransduction cascade components (cGMP-phosphodiesterase beta-subunit and cone-type cGMP-gated cation channel alpha subunit, Wada et al., 1998, 2000).

Axons of the hypothalamic VIP- and opsin-immunoreacting CSF-contacting neurons constitute a part of the tuberoinfundibular tract and project to the external layer of the median eminence (Yamada et al, 1982; Silver et al., 1988). In addition to the opsin-immunoreacting CSF-contacting neurons, GnRH (gonadotrop-releasing hormon) immunoreactive cells are also present in the preoptic area and lateral septum. VIP-positive nerve cells possibly corresponding to rhodopsin-positive neurons of the pigeon lateral septum form contacts (without synaptic specializations) with cell bodies and dendrites of gonadotrop-releasing hormone (GnRH)-positive neurons in the hypothalamus. Therefore, it was supposed that - besides a direct axonal projection to hypophysial portal vessels of the median eminence - these interactions are involved in mediating photoperiodic responses of the gonads in birds (Saldanha et al., 1994; Kiyoshi et al., 1998).

In **mammals**, light - mostly long wavelengths - penetrate the skull (Fig. 2d) in several species investigated (Ganong et al., 1963; Van Brunt et al., 1964; Hartwig and Van Veen, 1979), including human (Vígh, 1987; Vígh-Teichmann, 1991). Mammalian cerebral cortical tissue was found to respond to low-intensity visible light (Wade and Siekevitz, 1988), therefore an effect of light on the supposed encephalic receptors cannot be excluded.

The expression of *encephalopsin* as the first putative deep brain opsin in mammals, was detected in the preoptic area and paraventricular nucleus of the mouse. Encephalopsin is a newly identified family of mammalian opsins showing a high homology to vertebrate retinal and pineal opsins (Blackshaw and Snyder, 1999). As encephalopsin is expressed in several other areas of the brain (cerebral and cerebellar cortex, some striatal and thalamic neurons, interneurons of the ventral horn of the spinal cord) further studies are necessary to confirm its supposed role in extraretinal photoreception.

Blind **humans** with some degree of light perception mainly have normally entrained circadian rhythms, while subjects with no conscious light perception at all are more likely to exhibit disturbed circadian rhythms. Light-induced suppression of melatonin level in human is intensity- and wavelength-dependent. In contrast to extraocular light, ocular light exposure supresses the night-time level of melatonin (Zeitzer et al., 1997). Bilaterally enucleated patients show free-running melatonin rhythms, consequently, ocular light appears to be the major determinant of circadian rhythm in adults but that does not exclude the possibility that extraretinal photoreception are also present (Skene et al., 1999).

Pineal photoreceptors

As already mentioned, two pineal organs are present in the cyclostome lamprey and in bony fishes: the pineal and parapineal organ. In the cartilaginous fish (ray and

shark) and in urodelan amphibians (newt, salamandra) only a single organ was found, while in frogs there is a subcutaneous, extracranial frontal eye or frontal organ besides the intracranial pineal organ. Lacertilians also develop an extracranial parietal eye in addition to the intracranial pineal organ, while other reptilians such as the snakes have only a single intracranial pineal. Most birds and mammals, including human, exhibit only one intracranial pineal organ which is - in the case of the human pineal - the embryologically fused form of the originally double pineal anlages (Bargmann, 1943; Vollrath, 1961; Oksche, 1965; Kappers, 1968; Moller, 1974; Vígh-Teichmann et al., 1983a; Moller, 1986).

Submammalian pineal organs generally contain different types of photoreceptors. Morphologically, their outer segments are similar to those of cones of the lateral eye. However, only a part of them immunoreact with cone-opsins while others contain rod photopigments. We have to mention that antibodies specific for retinal rods of higher vertebrates may specifically mark cone photoreceptors of fishes and amphibians (Oksche and Hartwig, 1979; Ueck, 1986; Vígh-Teichmann et al., 1986; Röhlich and Szél, 1993). Mammalian pinealocytes develop photoreceptor outer segment-like cilia in some species only and are supposed to have lost their direct light sensitivity (Korf et al., 1998; Marone et al., 1999; Stechle, 2001). In the present chapter, we separately review data on pineal photoreceptors of various vertebrate classes. First, we briefly mention the ciliary photoreceptors of the lancelet.

In the **acranian lancelet** (*Branchistoma lanceolatum*) neither lateral eyes nor pineal organs, only encephalic photoreceptors are present (see the corresponding chapter). Indolamines were found in CSF-contacting neurons in several parts of the brain (Obermüller-Wilen and Van Veen, 1981). However, no melatonin receptors are present in this species (Vernadakis et al., 1998). Some photoreceptors (Satir cells) are sitting on the dorsal part of the brain vesicle, in a site similar to that of the pineal organs, therefore we can consider them the most primitive pineal photoreceptors (Vígh and Vígh-Teichmann, 1999).

Cyclostomes. In the hagfish (*Myxine glutinos*a), no pineal organ is present, but the small lateral eyes contain several photoreceptor lumina similar to the pineal organ of other vertebrates. The lateral eyes are covered by skin and muscles and cornea, lens and vitreous body are missing. Therefore, pineal-like rather than visual functions are attributed the rudimentary eyes. The outer segments of photoreceptor cells are immunoreactive with antisera raised against bovine rhodopsin (Vígh-Teichmann et al., 1984). The hagfish respond to light with withdrawal reaction culminating in burrowing (Brodal and Fänge, 1963).

In various lampetra-species (*Lampetra japonica*, *Lampetra planer*i, *Petromyzon marinu*s, *Geotria australis*) a pineal organ lies superficially, attached to the skull, and a parapineal organ is situated below it (Fig. 3).

The structure of the *pineal organ* of lampreys is the most simple among vertebrates. It is a small, flattened vesicle, its dorsal wall, called pellucida, is transparent and does not contain photoreceptors. The ventral wall, called retina, is thicker and contains photoreceptor cells and neurons, further, ependymal cells filled by light reflecting crystals in this species. The pineal lumen continues toward the brain into the pineal stalk which forms a small dilatation called atrium. Caudally, the lumen of the atrium disappears, and the stalk of the organ enters the brainstem in form of a solid pineal tract projecting to different brainstem areas (Cole and Yuson, 1982; Vígh-Teichmann et al., 1983b; Puzdrowski and Northcutt, 1989; Meyer-Rochow and Stewart, 1992a,b; Yáñez et al., 1993).

Electron microscopic and immunocytochemical studies revealed the presence of different kinds of photoreceptor cells functioning at different wavelengths. Most of the pineal outer segments bind rhodopsin antisera in the pineal retina and atrium (Fig. 4a,b), a finding that suggests the predominantly rod-like character of the organ (Vígh-Teichmann et al., 1983b, 1989; Kuo et al., 1988; Vígh and Vígh-Teichmann, 1988; Tamotsu et al., 1994a,b). A pineal-specific opsin - P opsin - gene has been isolated from the marine lamprey

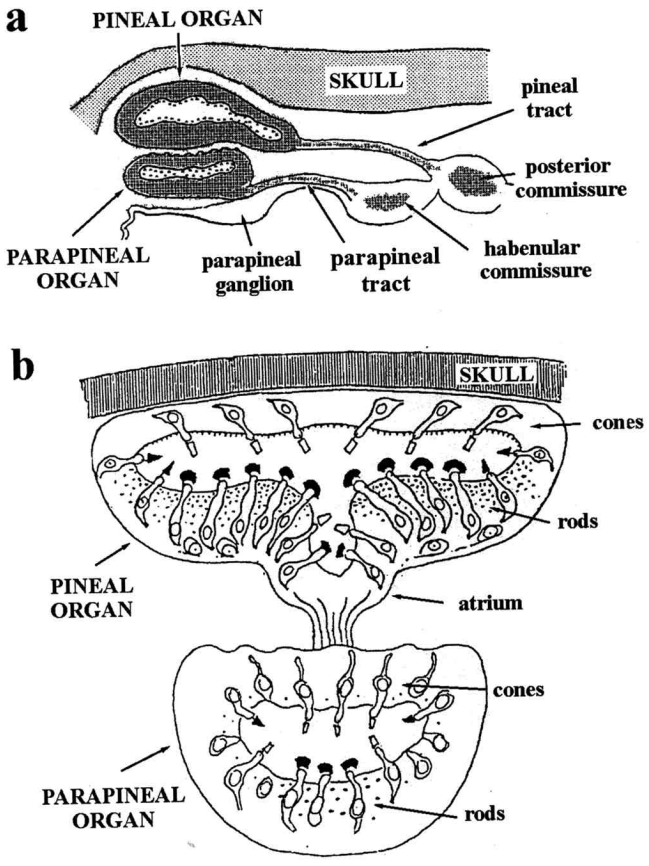

Fig. 3. Scheme on the pineal organs **(a)** and pineal photoreceptors **(b)** of the lamprey.

that is different from other opsins known in lower vertebrates (Zhang and Yokoyama, 1997; Yokoyama and Zang, 1997).

S-antigen and carbohyrates present in rods of the lateral eye were also demonstrated in the rod-like pineal photoreceptors. Visinin, characteristic of cone-type photoreceptors, as well as immunoreactive iodopsin are present in the lamprey pineal complex (pineal and parapineal organ). Alpha-transducin and arrestin, molecules of the phototransduction cascade have been identified by Van Veen and coworkers (1986). Vitamin A, the derivative of which is the chromophore of opsin, was demonstrated immunocytochemically in the outer segments and perikarya of photoreceptors. Experimentally, the pineal photopigment can be regenerated by photo-reisomeration (Vígh-Teichmann et al., 1983b, 1989; Meiniel and Meiniel, 1985; Kuo et al., 1988; Vígh and Vígh-Teichmann, 1988; Tamotsu and Morita, 1990; Tamotsu et al., 1994a,b).

Pineal photoreceptors also contain immunoreactive choline acetyltransferase and acetylcholinesterase. GABA-immunoreactive fibers originating from neuronal perikarya of the pineal stalk, and somatostatin immunoreactive neurons sitting in the dorsal wall of the pineal organ were also demonstrated in the lamprey (Meiniel, 1978; Meiniel and Hartwig, 1980; Cheung et al., 1990; Tamotsu et al., 1997, Pombal et al., 1999, 2001). Synaptic terminals of pinealocytic axons on secondary pineal neurons accumulate immunoreactive glutamate (Debreceni et al., 1997a). Some of the perikarya and axonal processes of photoreceptors and secondary neurons contain serotonin and hydroxyindole-O-methyltransferase, the ultimate enzyme of the melatonin synthesis (Joss, 1977; Meinel, 1978; Guerlotté et al., 1986).

In electrophysiological experiments, photoreceptors respond with hyperpolarization to light of $6x10^{-4}$ lux as a threshold which modulates the spike discharge of the secondary pineal neurons. The peak of the spectral sensitivity is at 505 nm in the larval and 525 nm in the adult animal, a result suggesting a change in the expression of opsin or in the chromophore of the visual pigment during metamorphosis. The presence of UV receptors having maximum sensitivity at 380 nm have also been postulated in the pineal organ (Morita and Dodt, 1973; Pu and Dowling, 1981; Morita et al., 1985, 1989, 1991a,b; Tamotsu and Morita, 1986; Uchida and Morita, 1990; Uchida et al., 1992).

Experimentally, it has been shown that melatonin is rhythmically synthesised in the lamprey pineal and is involved in the colour changes of the skin (Joss, 1973, 1977). Using in vitro autoradiography, melatonin binding sites were found in the preoptic nucleus and optic tectum (Vernadakis et al., 1998). There is a pineal-dependent circadian rhythmicity of locomotor activity in the lamprey (Morita et al., 1992).

The *parapineal organ* of the lamprey is smaller than the pineal, it exhibits a vesicle-like structure composed of a thin dorsal and a thickened ventral wall called dorsal and ventral "retina" respectively. The parapineal vesicle is located on a neuronal area called parapineal ganglion (Meiniel, 1969; Cole and Youson, 1982; Meyer-Rochow and Stewart, 1992a). The proximal portion of this parapineal complex is directly connected to the left habenular nucleus by the parapineal tract. As the pineal tract is connected to the right habenular nucleus, this arrangement may be the sign of the original bilateral position of the two supposed ancestral pineal organs.

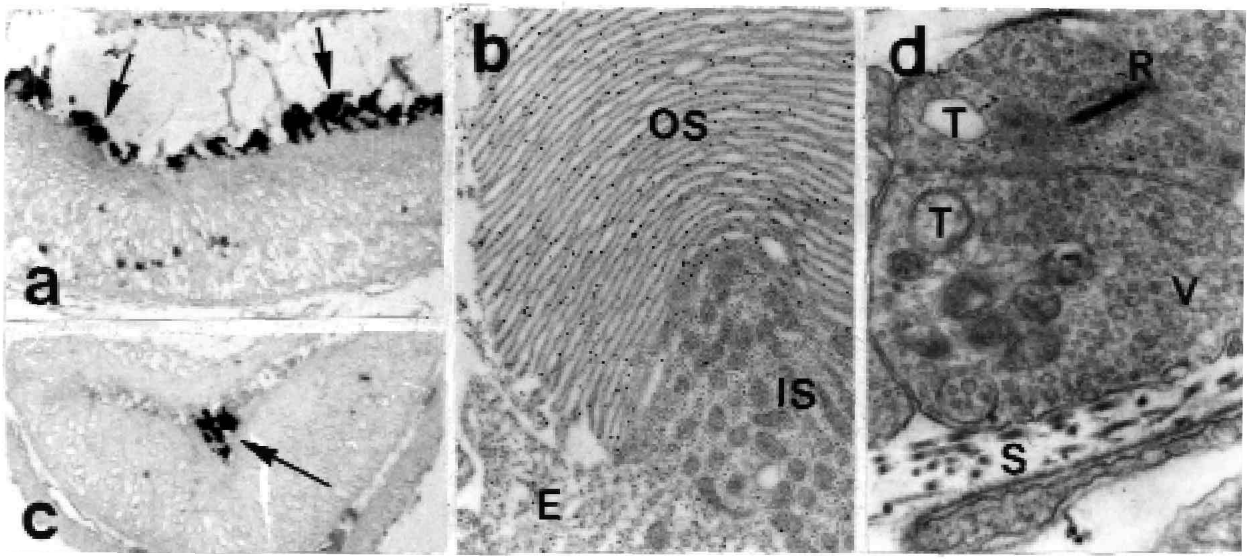

Fig. 4. a. Rodopsin immunoreaction (arrows) of the outer segments of the pineal photoreceptors in the lamprey. x 100. **b.** Rhodopsin-immunoreaction (black dots of immunogold particles) of the outer segment (OS) of the lamprey pineal photoreceptor. E: ependymal cell; IS: inner segment. x 12,000. **c.** Rhodopsin immunoreaction (at arrow) in the central photoreceptors of the parapineal organ of the lamprey. x 210. **d.** Axon terminals (T) of parapineal photoreceptors on the vascular surface (S) of the organ. R: synaptic ribbon; V: synaptic vesicles. x 24,000

Fibers arising from the bipolar parapineal cells and from the parapineal ganglion run in the left fasciculus retroflexus to the left interpeduncular nucleus. Nerve fibers reach the organ from the left habenula and bilaterally from the dorsal pretectum and subhippocampal nucleus (Yáñez et al., 1999; Pombal et al., 2001).

Electron microscopic and immunocytochemical studies revealed the presence of a high number of photoreceptors immunolabelled by cone opsins. Anti-rhodopsin binding outer-segments (Fig. 4c) were only found in the central portion of the ventral parapineal retina (Vígh-Teichmann et al., 1983b, 1989; Kuo et al., 1988; Vígh and Vígh-Teichmann, 1988, 1999; Tamotsu et al., 1990, 1994a,b; Yokoyama and Zhang, 1997). In addition to rod and cone opsins, alpha-transducin and arrestin involved in phototransduction cascade have also been found in the parapineal organ (Van Veen et al., 1986; Garcia-Fernandez et al., 1997). There are indoleamines in the parapineal cells, but catecholaminergic fibers are missing from the organ (Meiniel and Hartwig, 1980; Tamotsu et al., 1990, 1997).

The basal processes of the photoreceptor cells of the dorsal parapineal retina give rise to axons that terminate on the surface of the dorsal part of the organ (Fig. 4d) as neurohormonal endings (Vígh and Vígh-Teichmann, 1988; Vígh-Teichmann et al., 1989). Putative cholinergic cells were demonstrated by choline acetyltransferase immunocytochemistry (Pombal et al., 1999, 2001). Parapineal photoreceptors also contain immunoreactive glutamate (Debreceni et al., 1997a).

Not only are the afferentation and efferentation of the two organs different but also the photoreceptor types. In contrast to the pineal, containing predominantly rod-like photoreceptor cells, the parapineal organ can be regarded as a cone-dominant photoreceptor. The two organs may have by this complementary roles in the color change reaction and circadian locomotor activity mentioned in connection to the pineal organ (Vígh and Vígh-Teichmann, 1999).

In **cartilagineous fish** (Chondrichties) comprising Holocephala, raja species, and sharks, only one intracranial pineal is present (Fig. 5a). Pineal organs of these fishes are rather long tubes exhibiting a swelling on both ends. The two swellings may correspond to the two pineal organs of other species. Pinealofugal nerve fibers are well developed, but no specialized neurohormonal terminals were found (Altner, 1965; Rüdeberg, 1969; Ueck, 1981; Vígh-Teichmann et al., 1983a).

The habitat of the holocephalan ratfish (Chimera monstrosa) is in the 200 m deep mesopelagic twilight zone, but the opsin of blue-green sensitive chrysopsin - typical for the retina of deep sea fishes - could not be demonstrated in the pineal. However, in the lateral eye retina, the electron-lucent and electron-dense rods were shown to be chrysopsin-immunoreactive. Also S-antigen, known to bind specifically to photoexcited and phosphorylated rhodopsin, was detected in both the retinal and pineal cells (Vígh-Teichmann et al., 1990; Vígh-Teichmann and Vígh, 1994).

There are two types of intrapineal neurons in the ratfish, one of them is multipolar, the other one is bipolar and similar to CSF-contacting neurons by forming a luminal dendrite that bears a 9+0-type cilium (Fig. 5b). Axons of the pineal photoreceptor cells terminate on both pineal neuron types and the axons of the bipolar cells enter the pineal tract. Similarly to the lateral eye retina, pineal neurons also contain excitatory amino acids (Vígh-Teichmann et al., 1983a; Vígh-Teichmann and Vígh, 1986a,b; Vígh and Vígh-Teichmann, 1989a).

In the ray (*Raja clavata*), the proximal swelling, the terminal vesicle, as well as the narrow intermediate part of the pineal organ contains three types of photoreceptors. Most of them bind rhodopsin antisera, a result showing the predominantly rod-like character of the pineal organ. Some of the inner segments emit two cilia, a finding rather rare among the vertebrate pinealocytes (Vígh and Vígh-Teichmann, 1988). The axons of photoreceptor cells do not form neurosecretory endings, rather they terminate on dendrites of secondary pineal neurons by synaptic contacts. Another type of axon - presumably representing fibers of intrapineal or afferent brainstem connections - also terminates on

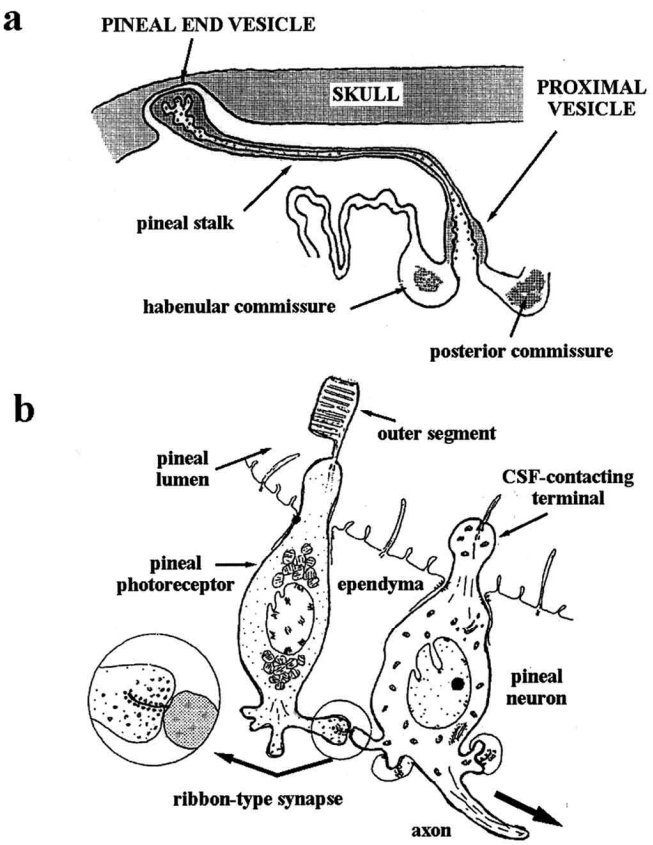

Fig. 5. Scheme on the pineal organ **(a)**, pineal photoreceptors and CSF-contacting-like pineal neurons of cartilagineous fish **(b)**.

intrinsic neurons (Vígh-Teichmann et al., 1983a; Vígh et al., 1995b).

There is only little information on the pineal organ of sharks. In *Triakis scyllia*, pineal nerve cells, which are similar to CSF-contacting neurons, were demonstrated to immunoreact with acetylcholinesterase and send one of their processes into the pineal lumen (Altner, 1965; Ueck and Kobayashi, 1979; Ueck, 1981). In elasmobranchs the pineal tract projects to serotonin- and encephalin-containing nuclei of the thalamus/pretectal-area, to the posterior tubercle and to the medial mesencephalic tegmentum. Further, there are pineal projections to the midbrain GnRH neurons which are primarily not hypophysiotropic in these animals (Mandado et al., 2001).

In **teleostean species** two pineal organs are present: the pineal and parapineal organ, both situated intracranially, one below the other.

The *pineal organ* has a long pineal stalk and a terminal enlargement attached to the meninges below the skull. Similarly to the pineal of cartilaginous fish, the pineal organ of the eel also forms a secondary, proximal thickening, both containing photoreceptors. In teleosts, particularly those living in the deep sea, the photoreceptor cells exhibit well-developed outer segments (McNulty, 1979, 1980; Herwig, 1980; Van Veen et al., 1980; Omura and Ali, 1981; Van Veen, 1982; Ali et al., 1988; McNulty et al., 1988; Goto et al., 1989; Gonzalez et al., 1990). Most of the outer segments react with rhodopsin- (Fig. 6a), or visinin antibodies (Vígh-Teichmann et al., 1980b, 1982, 1990, 1991b, 1992; Meyer-Rochow et al., 1999).

The cDNAs of the VA (vertebrate ancient) opsin family - mentioned in connection to the deep encephalic photoreceptors - were isolated and characterised from the pineal and retina of the carp and Atlantic salmon (Moutsaki et al., 2000; Philp et al., 2000a). In the zebrafish an opsin gene was found to be expressed in the pineal organ but not in the retina. The deduced amino acid sequence was found to be similar to rhodopsin of the zebrafish retina and named exo-rhodopsin (extra-ocular rhodopsin). The exo-rhodopsin gene was found in other teleosteans as well, showing that exo-rhodopsin may be a pineal opsin common in teleosts (Kojima and

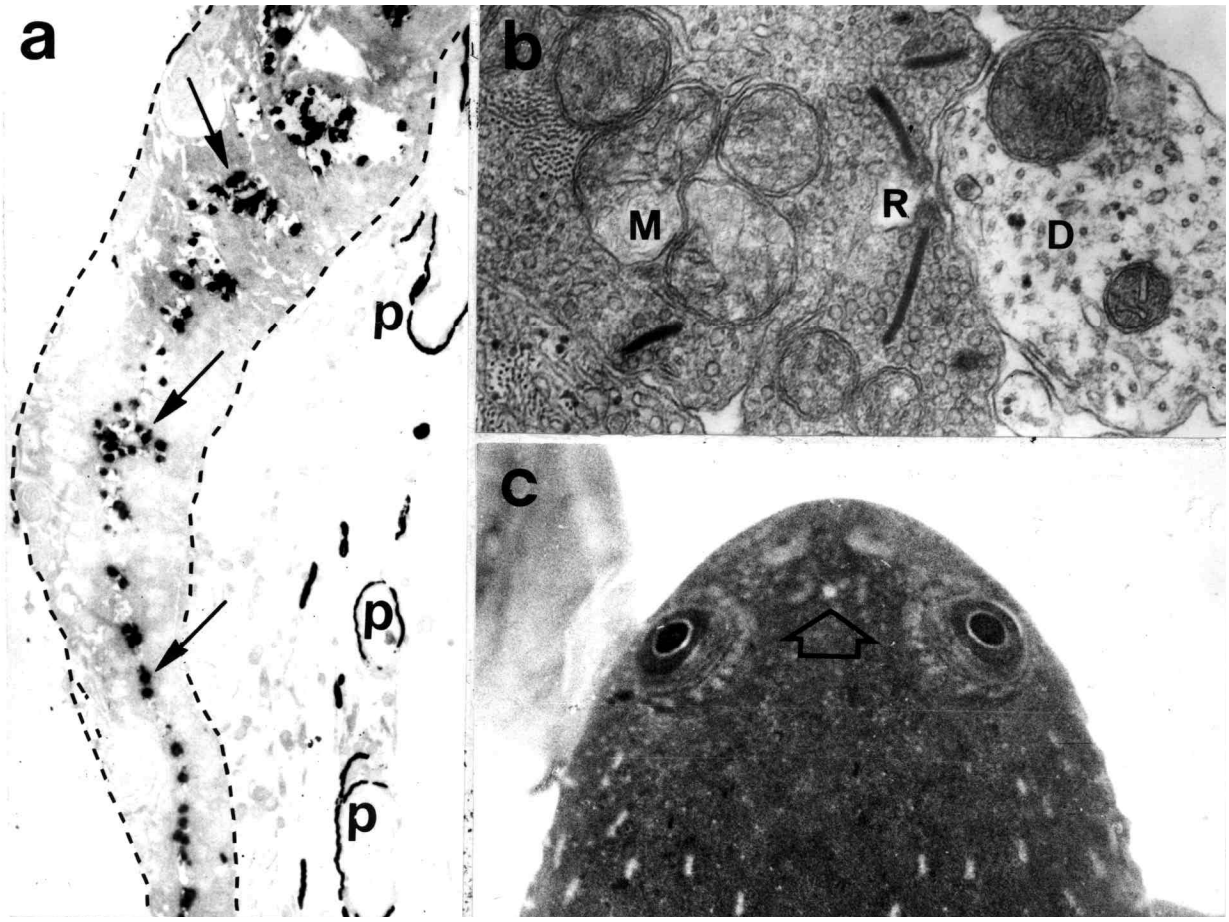

Fig. 6. a. Rhodopsin-immunoreacting outer segments (arrows) in the pineal organ (dotted) of the fish *Cyprinus carpio*. P: pigment cells. x 280. **b.** Synaptic ribbon (R) containing terminals of pinealocytes on the dendrite (D) of the secondary pineal neuron of the newt (*Pleurodeles waltlii*). M: mitochondria. x 49,000. **c.** The pigmentfree spot (arrow) above the frontal eye of *Xenopus laevis*. x 2

Fukuda 1999; Mano et al.,1999). Another opsin, called ERrod-like opsin (extraretinal rod-like opsin) was determined by Philp and coworkers (2000b) in the salmon and puffer fish.

In addition to opsins, S-antigen, FMRFamide, alpha transducin and serotonin immunoreactive cells were observed in the pineal organ of several species (Van Veen et al., 1984, 1986; Ekström and Meissl, 1990a; Kroeber et al., 1998). As a member of the photic signal transduction, immunoreactive cyclic GMP was localized in S-antigen containing pineal photoreceptors of the trout (Zipfel et al., 1999). The mRNAs of putative photoreceptor-specific guanylate cyclases were located to the pineal organ by in situ hybridisation and are supposed to participate in the phototransduction of pinealocytes in the Japanese medaka fish (Hisatomi et al., 1999).

Demonstrating a well developed neural efferentation, axons of pinealocytes form ribbon-containing terminals on secondary neurons, whose axons contribute to the pineal tract that connects the pineal organ to the brain stem (Ekström et al., 1967, 1987; Omura, 1979; Matsuura and Herwing, 1981; Vígh and Vígh-Teichmann, 1981; Ekström, 1984, 1987; Omura, 1984; Van Veen et al, 1984; Ekström and Korf, 1985, 1986a,b; Vígh et al., 1986a; Ekström and Meissl, 1990a; Joy and Agha, 1993; Yáñez et al., 1993; Jimenez et al., 1995; Yáñez and Anadon, 1998).

In electrophysiological experiments, the fish pineal was found to react to light stimuli directly and to operate both in dim and bright light. Light stimuli elicit intensity-grade hyperpolarization inhibiting the discharge of secondary neurons. The receptor cells produce constant amplitude responses during steady illumination and show spectral sensitivity peaks in the range of about 495 to 530 nm. The presence of several kinds of interneurons (cholinergic, GABA-ergic and substance P-containing), and further, a pinealopetal (noradrenergic and peptidergic) innervation was described by means of immunocytochemistry. Therefore, a complex integrative neuronal circuitry may be involved in the elaboration of neural signals to the brain (Dodt, 1963; Morita, 1966; Ekström et al., 1967; Omura and Ali, 1980; Ekström and Korf, 1986a,b; Meissl et al., 1986; Nakamura et al., 1986; Kusmic and Marchiafava, 1990, Meissl and Ekström, 1991; Meissl and Brandstattler, 1992; Marchiafava and Kusmic, 1993).

Immunoreactive hydroxyindole-O-methyltransferase (HIOMT), the enzyme that catalyses the final step in the synthesis of melatonin was exclusively associated with the photoreceptor cells in the pineal of chondrostean and teleostean fishes (Falcon et al. 1994). There are day/night variations and seasonal changes in the pineal melatonin content and in the activity of HIOMT enzyme. Calciproteins were found to regulate cyclic AMP content and melatonin production in pineal photoreceptors of the trout (Begay et al., 1994). Melatonin production may be modified by temperature as well (Birks and Ewing, 1986, McNulty et al., 1988; Max and Menaker, 1992). Rhythmic melatonin production of explanted fish pinealocytes in darkness show the presence of a cellular circadian system, but the expression of melatonin synthesis genes is not controlled by a circadian clock in all species (Bolliet et al., 1994, 1997; Coon et al., 1998; Falcon et al., 1998).

Opsin-immunoreactivity can already be demonstrated during ontogeny in the prehatching three-spined stickleback and charr embryos (Van Veen et al., 1984; Vígh et al., 1986a; Robinson et al., 1995). Similarly, in contrast to retinal photoreceptors appearing one day before hatching, pinel photoreceptors are already well developed 7 days before hatching in the rainbow tout (Omura and Oguri, 1993). The early development of the pineal photoreceptors preceding the retinal differentiation suggests a priviledged role for the fish pineal in the entrainment to the environmental photoperiod during embryonic life (Ostholm et al., 1987, 1988). There is a postmolt change in the pineal as well: in contrast to a high number of acetylcholinesterase-positive perikarya found in alevins and presmolts, no similar cells are present in the postmolt Pacific coho salmon, a phenomenon indicating a decrease of neural efferentation and a modification of pineal function in adult (Ostholm et al., 1992).

The *pineal apparatus* of fishes. In some species, especially in deep-sea fishes, a clear spot on the head is situated just above the pineal region, which acting as an optic diaphragm, allows pineal photoreceptors to percieve the direction of the light source (Holmgren, 1959). Moreover, in tunas and related scombrid fishes a "pineal apparatus" was described (Rivas, 1953), which conducts light through the skull to the pineal (van de Kamer, 1965). The pineal apparatus is a tube-like light channel. The "pineal tube" is surrounded by fat tissue and formed by frontal, suboccipital and alisphenoid bones. At the top of the pineal tube, there is a translucent, dermal tissue of pineal window. The base of the tube lies just above the pineal organ, which on the frontal part of the brain is positioned deep in the relatively large skull. The axis of the tube makes a 45° angle directed anteriorly to that of the body axis. The pineal apparatus may serve as a directional light receptor controlling phototactic movements.

The *parapineal organ* of teleosts is a small round body located on the left side of the brain above the epithalamus. The organ contains neurons, glial cells, and parapinealocytes of the photoreceptor-type. Their outer segments bind rhodopsin antisera, indicating the presence of rhodopsin-like visual pigment and thereby a light-percieving capacity. The parapineal tract originates from the neurons of the organ and connects it with the left habenular nucleus (Hafeez and Merhige, 1977; Van Veen et al., 1980; Vígh-Teichmann et al., 1980a,b, 1982; Van Veen, 1982). By means of specific antisera to retinal, S-antigen and alpha transducin, immunoreactive cells were observed in the parapineal organ of the rainbow trout and the European minnow (Ekström et al., 1987).

Parapinopsin, a newly identified opsin was localized to several parapineal cells, but only to some pineal cells of the channel catfish (Blackshaw and Snyder, 1997a). Parapinopsin was supposed to define a new family of photopigments that is not an orthologue of avian pinopsin and is divergent from any known vertebrate opsins, except VA (vertebrate ancient) opsin (Philp et al., 2000a,b). The presence of different opsins in the parapineal and pineal organs show, that similarly to the lamprey, the two pineal organs of bony fishes may be specialized to percieve different wave-lengths of light.

The central projections of the parapineal organ in the rainbow trout suggest a functional relationship to the limbic system (Yáñez at al, 1996, 1999).

The **pineal complex of amphibians** is formed by the frontal organ or frontal eye present in anuran amphibians, and by the pineal organ present both in anurans and in urodelans.

There is little information on the pineal organ of urodelan species (Fernandez Gonzalez, 1979; Gern and Norris, 1979; Kikuchi and Aoki, 1982; Maier and Singer, 1982, Pietsch and Schneider, 1985; Van Veen et al., 1986). In newts and salamanders, the pineal complex is represented by a pineal organ only. However, in the salamander *Hynobius dunni* the pineal complex consists of an anterior and a posterior portion. The anterior body appears to be homologous to the extracranial frontal organ of anurans and the posterior part represents the intracranial pineal organ (Takahama, 1993).

In *Ambystoma tigrinum* 150-190 photoreceptor cells were found in the pineal organ and approximately 70 intrapineal neurons. Consequently, axons of 2-3 photoreceptors are terminating on one secondary nerve cell on average. In all species investigated the photoreceptor cells are connected to dendrites of the nerve cells by ribbon-type synapses (Fig. 6b). Pinealocytes and pineal neurons contain immunoreactive glutamate (Vígh et al., 1995a,b). Some pineal photoreceptors send a long axonal process to neurons located within the area of the subcommissural organ. These extrapineal neurons emit pinealopetal fibers (Korf, 1976).

Immunoreactive opsin was found on the pineal outer segments in *Triturus vulgaris* (Vígh-Teichmann et al., 1980a,b; Vígh and Vígh-Teichmann 1981; Vígh et al., 1983). Recent studies on the pineal of the blind cave salamander (*Proteus anguinus*) have shown outer segments consisting of few photoreceptor membranes (Kos and Bulog, 1996, 2000). Immunocytochemistry with various opsin antibodies demonstrated the presence of only one type of opsin which was found to be red-sensitive (Kos et al., 2000).

Several axons were found in the pineal lumen to form synapses on the pineal ependyma in the newt *Pleurodeles waltlii*. Their postsynaptic cytoplasm contains myeloid bodies that are also present in the retinal pigment epithelium. Since the pineal ependyma contains vitamin A, as detected by immunocytochemistry, the ependymal cells can play a role in the chromophore metabolism - like the retinal pigment epithelium - of pineal photopigments. The innervating axons may control this ependymal function (Vígh-Teichmann et al., 1973, 1987, 1988).

Effects of photoperiod and pinealectomy on plasma melatonin level were studied by Gern and Norris (1979). The pineal organ may play a role in the skin camouflage reaction depending on an interaction between the direct and reflected light of salamander larvae (Pietsch and Schneider, 1985). An effect of shadowing the pineal region on the forelimb regeneration was also reported (Maier and Singer, 1982).

The extracranial *frontal eye* or frontal organ of frogs is located in the skin between and above the eyes in a pigment-free area (Fig. 6c) and thus may have some "directional light sensitivity" facilitating the detection of sites of direct solar irradiation and positive/negative phototaxis. The frontal eye is smaller than the pineal organ and encloses small lumina. Similarly to the pineal organ, in addition to nerve fibers and synapses it is composed of photoreceptor cells, glial elements, and secondary neurons. The organ is relatively large in larvae and serves as an underwater photoreceptor (Roberts, 1978; Eldred and Nolte, 1981; Vígh and Vígh-Teichmann, 1986).

There are rod- and cone-type photoreceptor cells of the frontal organ. Rod-type cells are characterized by a rhodopsin-immunopositive outer segment and by an electron-dense cytoplasm. Cone-type cells have a rhodopsin-immunonegative outer segment and electron-lucent hyaloplasm; some of them contain an oil droplet (Eldred and Nolte, 1981; Vígh-Teichmann et al., 1986, 1987, 1988, Korf et al., 1989; Okano et al., 2000). Immunoreactive bovine rhodopsin and iodopsin were found in the frontal organ of *Rana catesbeiana*, and HPLC analysis demonstrated the presence of 11-cis and all-trans retinal (Masuda et al., 1994; Yoshikawa et al., 1994).

In contrast to the pineal organ, which is predominantly a rod-type light-sensitive organ, the large number of cone-like photoreceptors found in the frontal eye indicates that it is the cone-type light perceptive capacity which is dominating in this latter organ. The basal, axonal processes of all photoreceptor types do not form neurohormonal endings; rather, they form pedicle-like terminals that synaptize with dendrites of secondary neurons of the organ. The axons of these neurons join to the frontal nerve and pineal tract. The neurons respond differentially according to the wavelengths of the light stimuli (Baumann, 1962; Hamasaki, 1970; Paul, 1972; Eldred et al., 1980; Vígh-Teichmann et al., 1980a,b; Korf et al., 1981; Vígh and Vígh-Teichmann, 1986, 1988, Ekström and Meissl, 1990b; Vígh-Teichmann and Vígh, 1990).

The *pineal organ* of anurans seems to be more differentiated than the fish pineal, since it is larger in size and its wall forms numerous side pockets (Fig. 7a). Immunocytochemistry with various antisera showed the presence of rods and cones in Rana species (Fig. 7b). By

high performance liquid chromatography (HPLC) 11-cis and all-trans retinal, as well as, 11-cis-3-dehydroretinal have been detected in the organ. Photoreceptors also show the presence of immunoreactive rod-type transducin, visinin (retinal cone-specific protein), S-antigen and vitamin A (Vígh et al., 1985; Van Veen et al., 1986; Vígh-Teichmann et al., 1986, 1987, 1988; Goto et al., 1989; Korf et al., 1989; Vígh-Teichmann and Vígh, 1990, 1992; Masuda et al., 1994; Yoshikawa et al., 1994; Okano et al., 2000).

The ultrastructural findings in the pineal organ are in accordance with electrophysiological data demonstrating neuronal responses with spectral sensitivities at various absorption maxima. The rod-like photoreceptors seem to correspond to those photosensory elements that produce inhibitory achromatic responses in secondary neurons at an absorption maximum of about 500 nm - a wavelength typical of rhodopsin. The two cone-like photoreceptors are thought to be identical to structures responsible for light perception in the orange (iodopsin) and ultraviolet-blue ranges of the spectrum (Dodt and Heerd, 1962; Dodt and Morita, 1964; Morita, 1965, 1969; Meissl and Dodt, 1981; Dodt and Meissl, 1982; Meissl and George, 1984; Vígh and Vígh-Teichmann, 1988, 1999).

Various types of pineal nerve cells were demonstrated in frogs by histochemical ACHE-reaction.

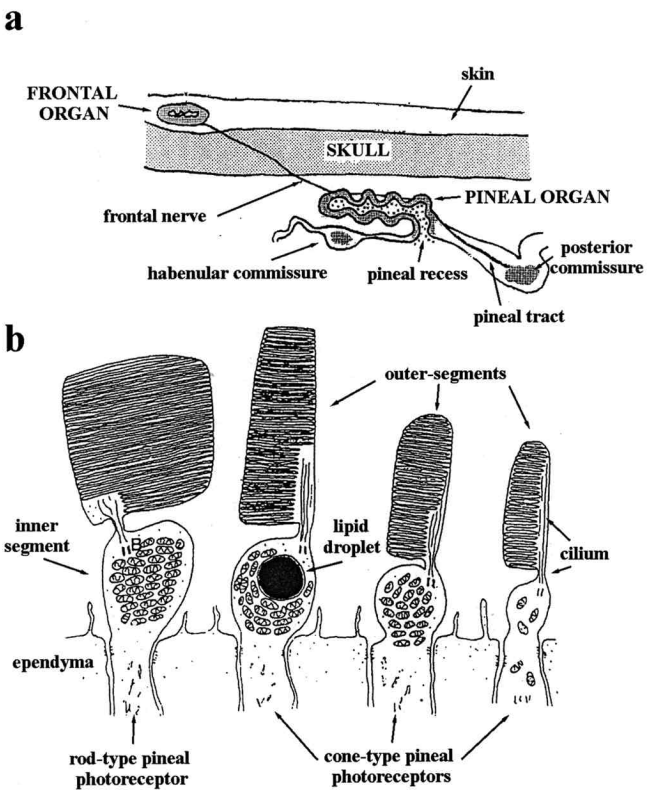

Fig. 7. Scheme on the pineal organs and photoreceptors of anurans. **a.** The extracranial frontal eye and the intracranial pineal organ. **b.** Photoreceptor-types of the frog pineal.

Some GABA immunoreactive perikarya of the pineal are thought to be inhibitory interneurons. Possibly, representing pinealopetal afferentation, axodendritic synapses are formed on dendrites of pineal neurons whose presynaptic axoplasm contains large granulated vesicles. Some of the afferent fibers immunoreact with FMRFamide antibodies and enter the organ via the posterior commissure (Wake et al., 1974; Ueck, 1979; Ueck and Kobayashi, 1979; Vígh-Teichmann et al., 1986; Ueck et al., 1989; Ekström and Meissl, 1990b; Ekström et al., 1990).

Using immunocytochemical methods, similar presynaptic accumulations of glutamate and aspartate were found in the synapses of pineal as well as retinal photoreceptors. Double label immunoreaction showed a colocalization of both amino acids. Glutamate and aspartate were also found in axons of pineal neurons. Accordingly, glutamate and aspartate were shown to exert an excitatory effect on achromatic light responses of pineal neurons. The centrally projecting neurons respond to all increases of ambient illumination with decreases in spontaneous firing of action potentials, a result showing that the pineal organ functions mainly as a luminosity meter. Some neural units respond in a wavelength-dependent manner (Meissl and George, 1984; Bonaventure et al., 1989; Ekström and Meissl, 1990b; Vígh et al., 1995a,b).

At the ventral surface of the frog pineal organ granulated profiles can be found resembling neurosecretory terminals, the possible morphological substrate of hormonal release. Supposedly, the color-change mechanism of the frog is related to a melatonin-dependent photoneuroendocrine regulation. There are several melanocytes above the pineal organ of the frog that in dark-adapted animals are in a contracted state. Melatonin-secreted at night by the pineal may have a contracting effect on these melanophores (Vígh and Vígh-Teichmann, 1986; Korf et al., 1989; Vígh-Teichmann and Vígh, 1990).

In the lumen of the pineal organ, macrophages can often be observed. In their cytoplasm, parts of outer segments exhibiting various degrees of disintegration can be detected by electron microscopy. Opsin-immunoreactive membranes are also frequently present among the phagocytized elements and indicate a shedding of photoreceptor lamellae of pineal outer segments, a phenomenon well known in the retina. Pinealocyte outer outer segments of the frog undergo a complete daily renewal (Hartwig and Baumann, 1984; Vígh and Vígh-Teichmann, 1988).

Reptilians have one or two pineal organs. Except for the alligators (Achrosauria) which lack pineal organs, most reptiles posses an intracranial pineal, and some of them (e.g. lacertilians) posses an extracranial parietal eye as well (Vivien-Roels, 1964, 1970; Van de Kamer, 1965; Collin and Kappers, 1968; Oksche and Kirschstein, 1968; Petit, 1968, 1971; Collin and Meiniel, 1971; Meiniel et al., 1973; Oksche and Hartwig, 1979; Roth et al., 1980; Dodt and Meissl, 1982; Kalsow et al., 1991;

Ohshima et al., 1999; Tosini et al., 2001).

The extracranial *parietal eye* (Fig. 8A) consists of a dorsal "lens" and a ventral "retina", both forming the wall of a vesicle-like organ that is situated below a transparent cornea. The "window" is formed by a membranous spot of the skull that is covered by a pigment-free area of the skin. In contrast to the intracranial pineal organ, the parietal eye is not lobulated, it contains photoreceptor cells, neurons and glial elements (Engbretson and Anderson, 1990; Engbretson and Linser, 1991). The parietal nerve connects the organ to the left habenular ganglion, then branches to symmetric pathways that lead to pretectal, thalamic, hypothalamic and telencephalic regions (Watson, 1979; Engbretson et al., 1981; Korf and Wagner, 1981; Vigh et al., 1997).

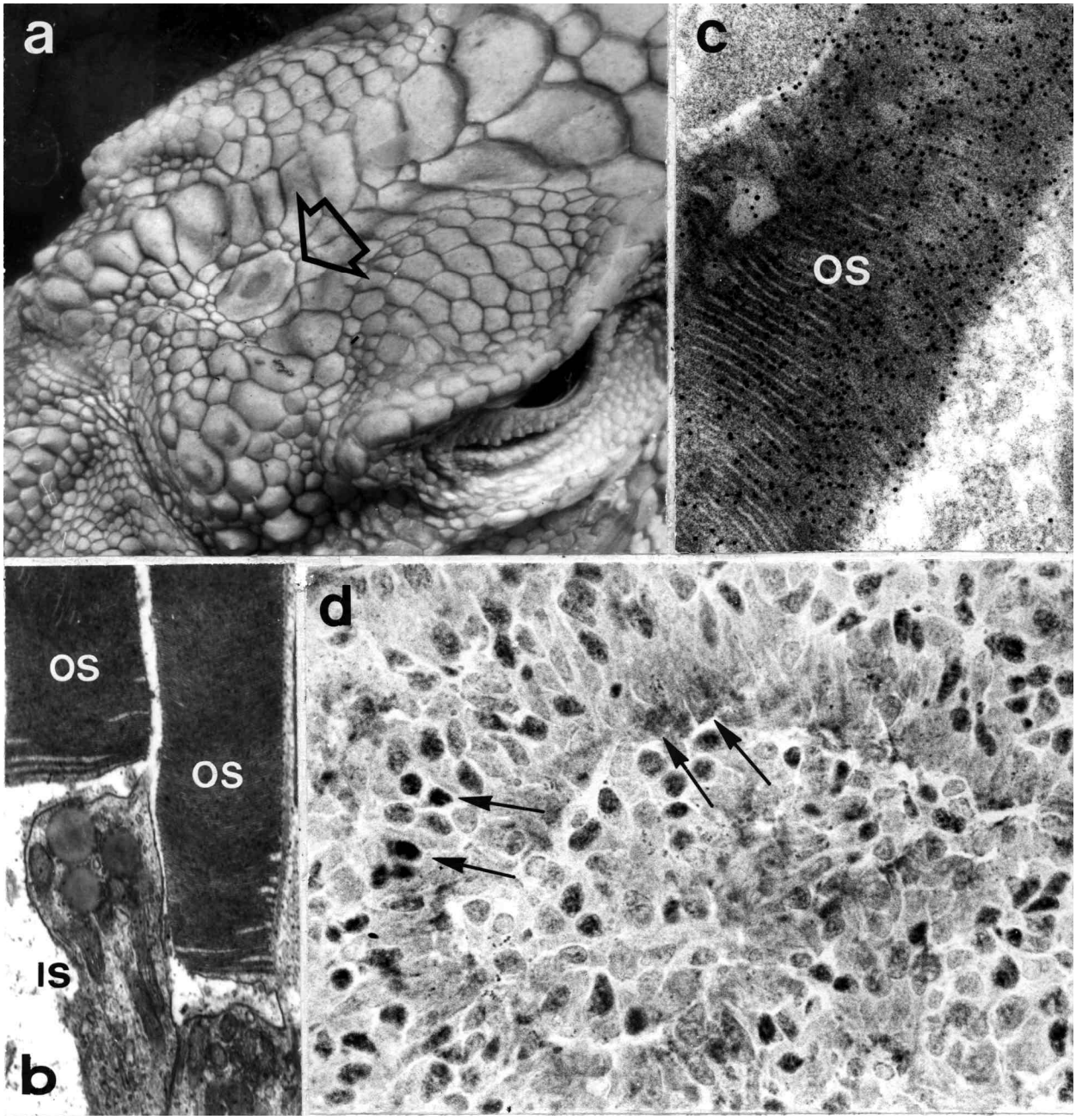

Fig. 8. a. The pariteal eye (arrow) of the leguan. **b.** Inner segments (IS) and the proximal part of the outer segments (OS) of the photoreceptor cells of the parietal eye of *Lacerta muralis*. x 18,600. **c.** COS-1 immunoreactivity (black dots of immunogold particles) of the outer segment (OS) of the small pineal photoreceptor of the lizard (*Lacerta agilis*). x 21,700. **d.** CRY1- immunoreacting nuclei and cytoplasm (arrows) among immunonegative cells in the pineal organ of the guinea fowl (*Meleagris gallopavo*). x 690

The photoreceptor outer segments are long (Fig. 8b), and are not normally stained with either anti-rhodopsin antisera or anti-chicken iodopsin antibodies. These structures also fail to react with avian pinopsin antibodies (Trost, 1954; Eakin et al., 1961; Gundy et al., 1976; Jenison and Nolte, 1979; Vígh-Teichman et al., 1980b, 1998a; Vígh et al., 1982; Foster et al., 1993; Masuda et al., 1994; Fejér et al., 1997; Debreceni et al., 1998). In *Anolis carolinensis* three visual opsin genes as well as p-opsin (a nonvisual opsin gene ortologous to chicken pinopsin) was found to be expressed in the parietal eye and pineal organ (Kawamura and Yokoyama, 1997, 1998). Photoreceptors synthesize new disk membranes and shed their tips which are then engulfed by luminal macrophages (Achmed and Engbretson, 1993).

Electrophysiological experiments demonstrated that similarly to the invertebrate photoreceptors and unlike the rods and cones of the lateral eye retina and pineal organs, the parietal eye photoreceptors respond with a depolarization to light under dark adapted conditions. Maximal spectral sensitivity of electroretinographic responses of the parietal eye were detected at 495 nm green- and 430 nm blue-light (Hamasaki, 1969; Solessio and Engbretson, 1993; Finn et al., 1997, 1998; Xiong et al., 1998; Solessio and Engbretson, 1999).

Parietalectomy or experimental shielding of both the parietal eye and the pineal organ modifies the behaviour and body temperature of lizards (Miller and Wolbarsht, 1962; Engbretson and Hutchison, 1976; Firth et al., 1980; Kulshreshtha and Khan, 1988; Phillips and Howes, 1988). An ultraviolet-sensitive mechanism was found in the parietel eye which may have a role in the thermoregulation of these cold-blooded animals by detecting areas of direct solar irradiation (Roth and Ralph, 1977; Jenison and Nolte, 1981). Lizards without parietal eyes are restricted to low latitudes, whereas lizards with parietal eyes are successful at higher latitudes as well (Gundy et al., 1976). Interactions of parietal eye and pineal organ are probably important in synchronizing several bodily functions with photoperiod (Engbretson and Hutchison, 1976). Removal of the parietal eye did not affect the pineal melatonin rhythm in *Anolis carolinensis* (Underwood and Calaban, 1987).

The light-sensitive intracranial *pineal organ* of reptiles is larger and more lobulated than in amphibians. Connected by a long narrow stalk to the epithalamus, it is attached to the inner surface of the skull. Reptilian pinealocytes form photoreceptor outer segments and are characterized by a large amount of granulated vesicles presumably serving for the storage of serotonin (see immunoelectronmicroscopy in birds). Pinealocytic axons form a synaptic ribbon containing terminals on dendrites of secondary pineal neurons. Neurohormonal teminals are rare on the vascular surface of the organ (Hamasaki and Dodt, 1969; Vígh et al., 1975; Haldar and Thapliyal, 1977; Vígh et al., 1982; Ohshima et al., 1999).

There is a considerable difference in the pineal structure between various reptilian groups.

In turtles - representing low-differentiated reptiles - one photoreceptor-type was identified in the pineal organ (Vivien-Roels, 1970; Collin and Meiniel, 1971; Mehring, 1972; Owens and Ralph, 1978). The outer segments contain immunoreactive rhodopsin, suggesting a rod-like light-perceptive function for the turtle pineal (Vígh and Vígh-Teichmann, 1981; Vígh et al., 1982).

Lacertilians have at least two type of photoreceptor cells: the "dark-type" has a large outer segment, while the less numerous "light-type" has a smaller outer segment. This latter structure is recognized by the cone-specific monoclonal antibody COS-1 (Fig. 8c): (specific for the red- or green-sensitive outer segments) and/or OS-2, another monoclonal antibody (Szél et al., 1986, 1988; Röhlich and Szél, 1993). The large outer segments often react with iodopsin and chicken pinopsin antibodies. Some pinealocytes show S-antigen immunoreactivity (Hafeez et al., 1987; Masuda et al., 1994; Vígh-Teichmann and Vígh, 1994; Fejér et al., 1997; Debreceni et al., 1998, Vígh et al., 1998a). In the pineal organ of *Anolis carolinensis* three visual opsins and one nonvisual opsin similar to the chicken pinopsin were found by Kawamura and Yokoyama (1997, 1998).

Immunoreactive glutamate and aspartate were found to accumulate not only in the presynaptic part of axodendritic synapses, but also in the neurohormonal terminals of pinealocytes. Therefore we assume that excitatory amino acids may play a role not only in the neural transmission, but, similarly to the neurohypophysis, in the neurohormonal efferentation of the reptilian pineal as well. The majority of the secondary pineal neurons are bipolar, while a few of them are multipolar cells. In their cytoplasm, granular vesicles of 150 nm in diameter were found (Vígh and Vígh-Teichmann, 1988; Vígh et al., 1995b, 1997; Debreceni et al., 1998).

The pineal was shown to influence circadian locomotor activity in the iguana and ruin lizard (Foa, 1991; Innocenti et al., 1993). Following pinealectomy, collared lizards (*Crotaphytus collaris*) select or prefer lower temperatures than controls (Firth et al., 1980). The pineal organ of *Anolis carolinensis* shows light-dependent daily cycles of melatonin synthesis (Underwood and Gross, 1982; Menaker and Wisner, 1983; Underwood and Hyde, 1989; Underwood, 1990). Melatonin treatment has an antigonadotropic effect in the tropical lizard *Calotes versicolor* (Haldar-Misra and Thapliyal, 1981).

In snakes (Natrix species) - representing a higher level of reptilian differentiation - the pineal organ differs from that of turtles and lacertilians studied so far. The organ is small, spherical and is attached to the internal surface of the skull. The pineal lumen is rather narrow and lined by ependymal cells. The pinealocytes give rise to double cilia. The distal portion of the cilia is thickened like a developing retinal outer segment and may contain vesicles. Serotonin and immunoreactive S-antigen were found in the pinealocytes. However, neither rhodopsin nor avian pinopsin were detected (Kalsow et

al., 1991; Fejér et al., 1997; Debreceni et al., 1998; Vígh et al., 1998a).

On the perivascular surfaces of the organ, two different types of neurohormonal terminals can be found: electron-dense, large-sized terminals containing granular vesicles of 150 to 200 nm in diameter and electron-lucent ones of smaller size containing few granular and many synaptic vesicles. The two types of neurohormonal terminals furnish morphological evidence for the presence of two different substances that may be released by the pineal. The vessels of the organ are not fenestrated but are accompanied by myelinated and unmyelinated nerve fibers (Vivien-Roels, 1964; Quay et al., 1968; Petit, 1971; Vígh and Vígh-Teichmann, 1988).

Most of the *bird species* have a single pineal organ that is fixed to the meninges of the skull and connected to the epithalamus by a long stalk. The avian pineal contains photoreceptors; it is the anatomical substrate of circadian clock mechanisms, and it also has a melatonin-producing capacity. Similar to the retinal photoreceptors, the avian pinealocytes are characterised by the presence of a paraboloid, they bear a photoreceptor outer segment that is small in the chicken, duck, sparrow and ostrich, whereas the guinea-fowl, pigeon, pheasant, quail, parrot or buzzard outer segments are more developed (Vígh and Vígh-Teichmann, 1974, 1988, 1999; Vígh et al., 1975; Vígh-Teichmann et al., 1980a; Korf and Vígh-Teichmann, 1984; Watanabe et al., 1985; Ohshima and Matsuo, 1989, 1991a; Araki et al., 1992; van't Hof and Gwinner, 1996).

In all species investigated so far, pineal outer segments are more differentiated in young animals than in adults, a phenomenon suggesting a role for the light-perception in the posthatching synchronization of internal biological rhythms to environmental light conditions (Moller and Moller, 1990; Ohshima and Hiramatsu, 1993; Csernus et al., 1998; Vígh and Vígh-Teichmann, 1999; Fejér et al., 2001a).

Opsin immunoreactive photoreceptor outer segments have first been demonstrated in the pineal organ of finch, parrot, canary, white leghorn chicken and pigeon (Vígh and Vígh-Teichmann, 1981; Vígh et al., 1982). Most of the outer segments react with anti-rhodopsin antibodies, while some of them are labelled by antibodies specific for iodopsin (Araki et al., 1992; Araki and Watanabe, 1996; Masuda et al., 1994; Yamao et al., 1999).

Pinealocytes also contain pinopsin, a pineal-specific opsin having a green-blue light sensitivity (Okano et al., 1994, 1997; Max et al., 1995; Kawamura and Yokoyama, 1996; Okano and Fukuda, 1997; Takanaka et al., 1998; Kawamura et al., 1999; Nakamura et al., 2001). The characteristics of pinopsin are different from the known retinal photopigments and the longer lifetime of the excited pinopsin molecule indicates that it has been adapted to measuring light intensities by the pineal organ (Nakamura et al., 1999). It is not yet known whether the same pinealocytes react with rhodopsin and pinopsin antisera. There might be two distinct subpopulations present (Fejér et al., 1997; Hirunagi et al., 1997; Vígh et al., 1998a; Yamao et al., 1999). A colocalization of pinopsin and G-protein alpha-subunits in the chicken pineal suggest that they are functionally coupled in the light-activated outer segments. Experimental evidence also shows that the pinopsin-triggered phototransduction pathway is mediated by the rod-type transducin alpha-subunit (Kasahara et al., 2000; Matsushita et al., 2000).

Visinin, a retinal cone-specific protein, as well as S-antigen, alpha-transducin, IRBP (interstitial retinol-binding protein), calmodulin, recoverin and 11-cis retinal - all being essential in the photochemical transduction - are present in the avian pinealocytes (Collin et al., 1986; Foster et al., 1987; Goto et al., 1989; Sun et al., 1991; Pochet, 1994).

Perikarya of pinealocytes bind antibodies against enzymes of the melatonin biosynthetic pathway (Guerlotté et al., 1988; Voisin et al., 1988; Greve et al., 1993). Hydroxyindole-O-methyltransferase (HIOMT) mRNA expression was demontrated in most pinealocytes of the chicken (Wiechmann and Craft, 1993; Wiechmann, 1996). The mRNAs of TPH (tryptophan hydroxylase), AANAT (arkylamine-N-acetyltransferase) and HIOMT exhibit a circadian rhythm entrained very early in the development (Bernard et al., 1999; Chong et al., 2000; Herichova et al., 2001).

Among Period gene homologs, the mRNAs of *qPer2* and *qPer3* show a circadian oscillation in the pineal and retina of the Japanese quail (Yoshimura et al., 2000). Recently, MAPK (mitogen-activated protein kinase) was reported to play a role in the photic entrainment and maintenence of the circadian oscillation of chicken pineal (Sanada et al., 2000; Hayashi et al., 2001). Immunoreactive cryptochrome (CRY1) localised in some pinealocytes (Fig. 8d) is supposed to participate in blue-light perception as well as in pineal clock function (Dávid et al., 2001).

The effector process of the avian pinealocytes has an axonal character and predominantly form neurohormonal endings on the basal lamina of the pineal vascular surface. Granular vesicles are the sites of serotonine accumulation in the neurohormonal terminals (Vígh and Vígh-Teichmann, 1988; Ohshima and Matsuo, 1991b). Exocytosis of vesicles was observed on pinealocytes of parakeet by Masson-Pévet and coworkers (1987).

Pinealocytic axons also form *presynaptic terminals* on secondary pineal neurons. These terminals, usually axodendritic or axosomatic in nature, contain several synaptic and granular vesicles. Synaptic ribbons are located near the thickened presynaptic membrane (Vígh-Teichmann and Vígh, 1994; Vígh and Vígh-Teichmann, 1998). Experimental studies demonstrated that the amount of the synaptic ribbons present in pinealocytes varies according to a day/night rhythmicity (Maitra et al., 1989; Robertson et al., 1990; Maitra and Vollrath, 1991). Excitatory amino acids, the transmitter substances of retinal photoreceptors, have also been demonstrated in the pinealocytes and their terminals (Vígh et al., 1995a-

c; Manzano et al., 1996).

Neuronal perikarya were first demonstrated in birds by means of histochemical acetylcholinesterase reaction (Ueck and Kobayashi, 1972) and electron microscopy (Korf and Vígh-Teichmann, 1984). They contain neuron-specific enolase and are located near the external surface of the wall of the pineal tissue. Some of these are bipolar, while others are multipolar neurons. Not evenly distributed in the whole organ, they are more numerous in its proximal part and in the pineal stalk (Sato et al., 1995). The intrapineal AChE-reacting neurons were reported to decrease in number during the post-hatching development of the quail and chicken, a result indicating the decrease of neural efferentation in the adult organ (Ueck and Kobayashi, 1972; Sato and Wake, 1984). Axo-somatic synaptic terminals, different from those of pinealocytic axons also connect these neurons. They may represent interneuronal connections of pineal neurons or terminals of pinealopetal fibers. Electrophysiological data confirm the central innervation of the pineal organ via the habenular nuclei (Demaine and Semm, 1984; Semm and Demaine, 1984).

As demonstrated with light-microscopical methods, noradrenergic nerve fibers originating from the superior cervical ganglion reach the pineal organ in birds (Hedlund and Nalbandov, 1969; Ueck and Kobayashi, 1972, 1979; Zeman et al., 1992). Sympathetic fibers play a different role in birds than in mammals. In the latter animal group sympathetic fibers were found to synchronise the pineal rhythm of melatonin synthesis to environmental light periods (Wiechmann and Graft, 1993; Korf, 1994, 1996; Mess et al., 1996; Moore, 1996; Csernus et al., 1998). Not involving the superior cervical ganglion, an entrainment pathway has been postulated between the eyes and the pineal in the quail (Barrett and Underwood, 1991, 1992). Experiments in birds show that VIP (vasoactive intestinal protein)- and histamine-containing nerve fibers may play a role in circadian pineal rhythmicity (Pratt and Takahasi, 1989; Zatz et al., 1990; Nowak and Sek, 1994). Perivascular catecholamine-containing nerve fibers were reported to penetrate from the interfollicular septae to the neuroepithelial tissue of the pineal (Sato and Wake, 1984). Using tyrosine hydroxylase immunofluorescence, catecholaminergic fibers were demonstrated to increase in number during postembryonal development of the chicken, thus indicating a functional modification between post-hatching and adult pineals (Robertson et al., 1990).

Intracellular calcium-binding proteins were immunohistochemically detected in the chick pineal organ (Korf et al., 1992; Bastianelli and Pochet, 1994a,b; Pochet et al., 1994). The fine structural localization of free calcium ions in the pineal organ was demonstrated by the pyroantimonate precipitation technique, and it was found that in some birds, free calcium ions may form corpora arenacea-like concrements, the occurance of which is well known in mammalian and human pineals (Vígh et al., 1998b).

The *mammalian pineal* is generally considered a gland ("pineal gland") secreting melatonin, the production of which is inhibited by environmental light percieved by the retina and mediated via the suprachiasmatic nucleus and sympathetic fibers (Wurtman et al., 1964; Kappers, 1968; Vollrath, 1981; Foster et al., 1989; Karasek and Reiter, 1992; Korf, 1994, 1996; Kramm et al., 1993; Korf et al., 1998; Stehle et al., 2001). Since most authors deny the direct light sensitivity of pinealocytes, below we summarise only those characteristics of photoreceptors that are preserved in mammalian pinealocytes - mainly in postnatal age - with the aim to generally compare them with the deep encephalic and nonvisual retinal photoreceptors.

In some mammals such as the marsupial opossum, the insectivorous hedgehog, bat (*Nyctalus noctula*) and ferret, pinealocytes develop photoreceptor inner segments and outer segment-like structures especially in young animals (Fig. 9a). The outer segments are formed by 9+0-type cilia marking the receptor pole of mammalian pinealocytes. The effector pole is formed by an axon-like, ramifying process that terminates on the vascular surface of the organ or, on secondary pineal neurons by ribbon-type synapses (Pévet et al., 1977; Vígh et al., 1986b; Vígh and Vígh-Teichmann, 1988, 1989b, 1992b, 1999; Vígh-Teichmann and Vígh, 1992; Vígh and Vígh-Teichmann, 1993; Vígh, 1994; Vígh and Quay, 1989; Tosini et al., 2000).

Several molecules of the phototransduction cascade are present in mammalian pinealocytes and these are thought to take part in cellular functions other than photoreception (Korf, 1996). The perikarya or cell membranes of some pinealocytes immunoreact with rod-opsin antisera (Fig. 9b), while other cells proved to be negative (Korf et al., 1985; Vígh-Teichmann et al., 1993). About 25% of the pineal cells in the pigmented mice show rod opsin immunoreactivity, but in absence of retinals, it was not considered a functional photopigment (Kramm et al., 1993).

Rat pineals also express protein kinases that are identical to the corresponding rod photoreceptor rhodopsin kinases. In addition to rod opsin, a putative blue cone opsin is also expressed in the pineal of rat (Zhao et al., 1997). Recoverin, a calcium-binding protein, was found in the pineal of rat and sheep. Recoverin activates guanyl cyclase in retinal photoreceptors when intracellular calcium level decreases upon photoexcitation (Korf et al., 1992).

Some pineal cells contain IRBP (interstitial retinol-binding protein), while others synthesize CRA1BP (cellular retinal-binding protein), a molecule homologous to that found in Müller cells and pigment epithelial cells (Bridges et al., 1987). Retinoids have been demonstrated in the bovine pineal (Tsin et al., 1989). An enzyme similar to cone phosphodiesterase, but distinct from that of rods was found in rat and bovine pineals by Carcamo and coworkers (1995).

Electrophysiological data show light sensitivity of rat pineal that was considered partially dependent upon

the function of the retina (Barajas-López et al., 1987).

As already mentioned, the photoreceptor characteristics of mammalian pineal are more pronounced in young animals than in adults. In situ hybridization showed the expression of compounds in the rat pineal organ to reconstitute a complete

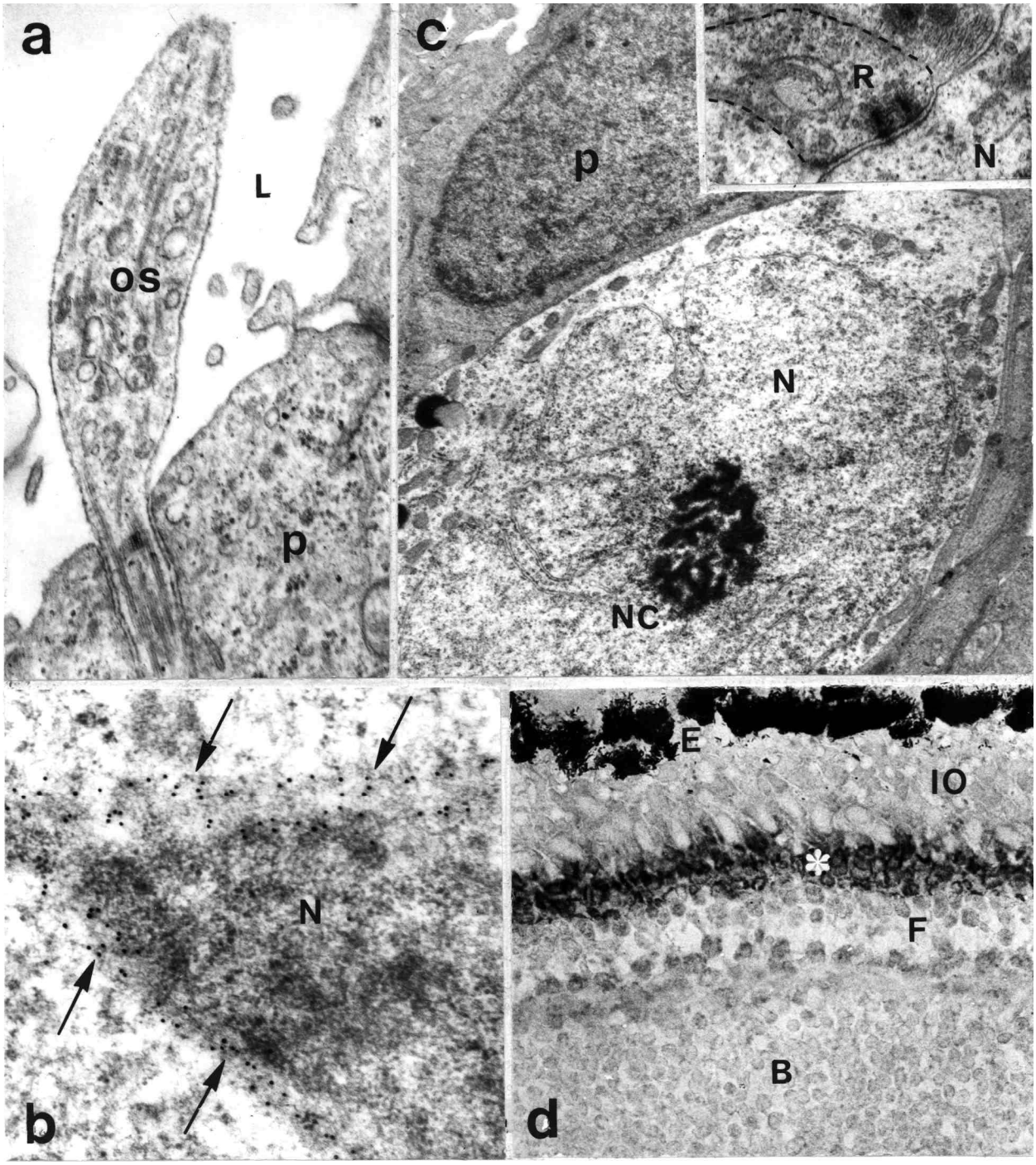

Fig. 9. a. Photoreceptor outer-segment-like cilium (OS) of the pinealocyte (P) of the young ferret (*Putorius furo*), x 16,400. **b.** Opsin immunoreactivity (black dots of immunogold particles at arrows) of the pinealocyte of the gerbil (*Meriones unguiculatus*). N: nucleus. x 30,000. **c.** Neuronal perikaryon (N) of the pineal organ of the cat. NC: nucleolus; P: pinealocyte. x 9,900. Inset: synaptic ribbon (R) containing pinealocytic terminal (cell membrane dotted) on the intrapineal neuron of the mink (*Mustela vison*). N: part of the pineal neuron. x 38,000. **d.** Immunoreactive CRY1 in the retina of the guinea fowl (*Meleagris gallopavo*). White asterisk: strongly immunoreacting layer of photoreceptor cells (F). B: layer of bipolar cells; E: pigment epithel; IO: inner- and outer segments of photoreceptors. x 470

phototransduction pathway. The highest density of cone-specific elements was found in the neonatal pineal (Blackshaw and Snyder, 1997b). Zweig and coworkers (1966) were the first to report on light-induced regulation of serotonin level in the pineal organ of neonatal rats. Sympathectomy carried out in the neonatal pineal cannot abolish light entrainment in the first weeks of life, in contrast to later stages, suggesting a photosensitive activity of the neonatal pineal organ of the rat but not in adult (Machado et al., 1969a,b). Other experiments showed that illumination in bilaterally enucleated neonatal rats reduced pineal N-acetyltransferase activity via an extraretinal mechanism (Torres and Lytle, 1990). The phosphodiesterase activity in rat pineals was found to decrease with age similarly to the somatostatin immunoreacting pineal cells of the pig (Przybylska-Gorowitz et al., 2000). Melatonin synthesis in pineal cell cultures of neonatal rats was supressed by light in contrast to pineals explanted at 5, 7 and 9 days of age (Tosini et al., 2000).

There are neuronal perikarya in the mammalian pineal organ (Fig. 9c). Synaptic ribbon-containing terminals of pinealocytes as well as common axons form synapses on the dendrites of pineal neurons (Levin, 1938; Vígh-Teichmann et al., 1991a). Besides synaptic vesicles, pinealocytic terminals contain synaptic ribbons and are glutamate- and aspartate-immunoreactive. These results show that mammalian pineal nerve cells represent secondary neurons like those present in the submammalian photoreceptor pineal organs or in the lateral eye retina. Some of the neuronal perikarya express GABA and/or somatostatin, substance P, glutamate and aspartate as demonstrated by immunocytochemistry (Matsushima and Reiter, 1978; Vígh-Teichmann et al., 1991a; Ichimura, 1992; McNulty et al., 1992; Matsushima et al., 1994; Vígh et al., 1995c; Debreceni et al., 1997b).

Axons of pineal neurons constitute a pineal tract running to habenular and other brain stem nuclei. These morphological data show that besides a hormonal output, there is a neural efferentation in the mammalian pineal organ that - similarly to retinal light conducting pathway - apparently uses glutamate and aspartate as synaptic mediators (Krstic and Nicolas, 1992; Redecker and Veh, 1994; Vígh et al., 1995c; Manzano e Silva et al., 1996). A central innervation of the pineal organ was demonstrated via the pineal stalk (Moller and Korf, 1983, 1987; Moller et al., 1993; Sakai et al., 2001).

Autonomic fibers reach the mammalian pineal by the so-called conarian nerves. Some of these nerves contain tyrosine hydroxylase indicating their noradrenergic character. Noredranergic and NPY (neuropeptide Y) immunoreactive fibers of the nerve originate from the superior cervical ganglion. Substance P and CGRP (calcitonin gene-related peptide) immunoreactive peripheral fibers originate from the trigeminal ganglion, while VIP (vasoactive intestinal polypeptide) containing nerves takes its origin in the pterygopalatine ganglion. Cholinergic fibers originate from peripheral parasympathetic ganglia as well as from the brain (Matsushima and Reiter, 1978; Shiotani et al., 1986; Matsushima et al., 1994, 1999; Moller et al., 1985, 1996; Kado et al., 1999; Phansuwan-Pujito et al., 1999). Some of the autonomic fibers were traced to precapillary arterioles of the pineal organ, where they form vasomotor-type nerve terminals on smooth muscle cells. The different fiber-types may represent vasoconstrictor, vasodilator or vasosensor elements, respectively (Vígh and Vígh-Teichmann, 1992b, 1999; Vígh et al., 2001).

The **human pinealocytes** also preserved some photorecepor characteristics, e.g. the presence of photoreceptor-specific molecules. Rhodopsin, recoverin (a retinal calcium-binding protein), S-antigen and peripherin have been demonstrated immunocytochemically in human pinealocytes. In pineal parenchymal tumours, the expression of several photoreceptor-, glial- and neuronal proteins such as rod-opsin, cone-opsin, S-antigen, IRBP (interphotoreceptor or retinol-binding protein) and cellular retinaldehyde-binding protein were also reported. Further, immunoreactive glutamate was found in human pinealocytic processes (Parentes et al., 1986; Huang et al., 1992; Korf et al., 1992, Lopes et al., 1993; Lerchl et al., 1998; Vígh and Vígh-Teichmann, 1999).

Human pineals also express protein kinase identical to the corresponding rhodopsin kinase of rod photoreceptors. The deduced amino acid sequence of the human rhodopsin kinase has an 84% sequence similarity to that of the bovine retinal enzyme. Using immunocytochemistry, rhodopsin and rhodopsin kinase were found to be co-localized in human pinealocytes (Zhao et al., 1997). As already mentioned, light penetrates the skull not only in various mammals but also in human.

Several neurons have been demonstrated by silver impregnation in the human pineal. The neuronal perikarya contain immunoreactive enkephalin, they are mostly multipolar cells and their axons form small bundles running to the medial habenular nucleus, a pattern indicating the existence of a neural efferentation for the human pineal (Moore and Sibony, 1988; Vígh and Vígh-Teichmann, 1992a; Vígh et al., 1998a, 2001).

Nonvisual retinal photoreceptors

The lateral eye retina is known to function as a light-based "visual locator" of environmental objects, a role allowing for a quick orientation in the biotop. To serve as a screen for decoding two-dimensional images of the environment, it remained unfolded during evolution. An unusual, pineal organ-like follicular organization suggesting a predominantly nonvisual, photodesitometer-like function, was found in the lateral eye of the hagfish and megachiropteran bats (Vígh-Teichmann et al., 1984; Fejér et al., 2001b).

In the nonvisual function of the retina, light-dark cycles set a circadian clock also present in the retina. Neither rods nor cones seem to be required for nonvisual

retinal functions, therefore the presence of some additional retinal photoreceptors, was postulated. Melanopsin and the blue-light absorbing vitamin B-based cryptochromes demonstrated in the retina may represent an additional photoreceptive molecule (Friedman et al., 1999; Lucas and Foster, 1999a,b; Lucas et al., 1999; Hall, 2000; Provencio et al., 2000, Sancar, 2000; Selby et al., 2000). Accordingly, Cryptochrome 1 (Fig. 9d) was immunocytochemically localized to a small subpopulation of retinal photoreceptor cells (Dávid et al., 2001).

Being simular to CSF-contacting neurons, some bipolar cells of the retina form ciliated dendrite terminals, the so-called "Landolt's clubs". These structures protrude into the interphotoreceptor space derived from the embryonal optic ventricle, a diverticle of the third cerebral ventricle. Landolt bipolars produce new photoreceptors during retinal regeneration in newt (Grigorian et al., 1996). They also may represent potential elements of nonvisual photoreception (Vígh et al., 1983; Vígh and Vígh-Teichmann, 1989a).

Retinal light periodicity is primarely important for proper retinal functions and regulates, among others, rod-cone dominance, ERG rhythms and retinomotor movements including elongation of cones, contraction of rods as well as the aggregation of pigment granules in the dark (Burnside et al., 1983; Zaunreiter et al., 1998; Manglapus et al., 1999; McGoogan and Cassone, 1999; Anderson and Green, 2000).

Nonvisual retinal photoreception also mediates photic entrainment of ocular melatonin production (Morell, 1996; Cahill and Hasegawa, 1997). An indoleamine-containing retinopetal pathway originating from the preoptic area and suprachiasmatic nucleus may also be involved in retinal melatonin synthesis (Schutte, 1995). Since melatonin receptors are present in the retina and retinal melatonin does not contribute to the circulating levels, it probably acts locally as a neuromodulator (Tosini, 2000). The antioxidant effect of melatonin may exert protective actions against light-induced oxidative processes in photoreceptors (Marchiafava and Longoni, 1999). Further, it seems to influence the volume of the ocular fluid and the function of the Harderian gland (Dhanaraj, 1995).

In the chicken retina, the mRNAs encoding the three key enzymes of melatonin synthesis, TPH (tryptophan hydroxylase), AANAT (asrkylamine-N-acetyl-transferase) and HIOMT (hydroxyindole-O-methyl-transferase) are expressed in a day/night rhythm (Bernard et al., 1999). The mRNA of HIOMT catalysing the final step in melatonin synthesis was found in yet unidentified subpopulation of retinal photoreceptors (Wiechmann and Craft, 1993; Wiechmann, 1996). In most vertebrates melatonin production of the retina is controlled by both circadian clock and light-dark cycles. In the trout retina, however, the expressoin of the gene of AANAT1 is regulated exclusively by light conditions (Mizusawa et al., 2000). Tryptophan utilized in the biosynthesis of melatonin was found in the photoreceptors and radial glial cells (Pow and Cook, 1997). Red light suppresses melatonin synthesis both in normal rats and in animals with retinal degeneration (Poeggler et al., 1995). In rodents ultraviolet light can also suppress nocturnal melatonin release (Amir and Robinson, 1995).

The molecular clock of the retina is driven by a number of genes such as clock, period, and crys. In the eye of bird mRNAs of *qPer2* and *qPer3*, homologues of clock and period, show circadian oscillation. Morover, *qPer2* is induced by light (Yoshimura et al., 2000). The mRNA of nocturnin, a circadian clock-regulated gene is expressed in retinal photoreceptor cells of *Xenopus* (Liu and Green, 2001). As photoreceptor molecules, cryptochromes are also part of the pacemaker mechanism in Drosophila. Humans and mice have two cryptochrome genes, cry1 and cry2 expressed in the retina (Griffin et al., 1999; Lucas and Foster, 1999b, Hall, 2000; Kobayashi et al., 2000, Lowrey and Takahashi, 2000). Three cryptochromes are rhythmically expressed in *Xenopus laevis* retinal photoreceptors (Zhu and Green, 2001). Using in situ hybridization and immunocytochemistry, cryptochromes were localized in a subgroup of retinal photoreceptors and in the retinal bipolars and ganglion cells (Miyamoto and Sancar, 1998, 1999; Dávid et al., 2001).

A nonvisual *retinohypothalamic connection* that projects to the suprachiasmatic nucleus originates from diffusely distributed small retinal ganglion cells. Amacrine cells are supposed to mediate or contribute to circadian responses to light. Retinal afferents also were traced to the anterior medial preoptic nucleus, the intergeniculate leaflet and lateral habenular nucleus. Substance P containing retinal fibers run to the olivary pretectal nucleus (Magnin et al., 1989; Moore and Speh, 1994; Reuss and Decker, 1997; Provencio et al., 1988).

The *suprachiasmatic nucleus* as a primary pacemaker drives daily rhythms of behavioral and physiological activity and is entrained by photic phase-shifts mediated by the retinohypothalamic tract. Hypothalamic brain areas similar to the suprachiasmatic nucleus of humans and mammals exist in vertebrates from fishes up to birds (Tilgner et al., 1990). The presence of VA opsin in the suprachiasmatic nucleus of fishes suggests that the suprachiasmatic pacemaker of higher vertebrates may originate from deep encephalic photoreceptors of lower vertebrates. Photic information is indirectly conveyed from the retina to the suprachiasmatic nucleus by the geniculo-hypothalamic tract containing GABA and neuropeptide Y. Nuclei of superior colliculus afferent to lateral geniculate nucleus are also components of the circadian rhythm system (Shinohara et al., 1993; Marchant and Morin, 1999). The output of the suprachiasmatic nucleus is principally directed to other hypothalamic nuclei, the middle thalamus and the basal forebrain (Moore, 1997).

The mammalian circadian clock system contains a core circadian rhythm generating a mechanism formed by an autoregulatory transcriptional feedback loop. Gene

mutations that modify circadian phenotype indicate the role of some genes such as *clock*, *bmal1* in the circadian oscillation (Akijama et al., 1998; Cermakian et al., 2000; Ripperger and Schibler, 2001). Two transcription factors CLOCK and BMAL1 (Brain-Muscle-Arnt/aryl hydrocarbon receptor nuclear translocator/-like protein), drive transcription of three period and two Cryptochrome-genes. The protein products of these genes participate in a negative feedback complex inhibiting CLOCK and BMAL1. "Slave" circadian timekeepers reside in most body cells of mammals; the suprachiasmatic nucleus as a master pacemaker synchronizes peripheral clocks via neuronal and hormonal effects. Restricted feeding can uncouple peripheral oscillators from the suprachiasmatic pacemaker (Vitaterna et al., 1994; Akijama et al., 1998; Cermakian et al., 2000; Ripperger and Schibler, 2001).

Circadian rhythms are already present during fetal life in several mammalian species. Direct fetal light perception may reinforce maternal entraining signals during the prenatal period (Weaver and Reppert, 1989; Torrealba et al., 1993).

A polysynaptic pathway is supposed to transmit information from the suprachiasmatic nucleus to the pineal organ via the paraventricular nucleus, the intermediolateral column of the upper thoracic cord and the superior cervical ganglion (Teclemariam-Mesbach et al., 1999).

General conclusions

We summarised and compared data on the nonvisual photoreceptors of the deep brain, pineal organs and lateral eye retina, disregarding light-sensitive elements like meningeal and cutaneous melanocytes, retinal pigment epithelium or iris, or the visual photoreceptors of the retina.

The *deep brain photoreceptors* of vertebrates studied so far, are hypothalamic and septal nuclei of the periventricular cerebrospinal fluid (CSF)-contacting neuronal system. Already present in the prochordate lancelet ("protoneurons"), CSF-contacting neurons line the wall of the brain ventricles and send ciliated dendritic processes into the CSF (Vígh et al., 1969, 1975, 1983; Vígh-Teichmann et al., 1980a,b; Vígh-Teichmann and Vígh, 1983, 1989; Vígh and Vígh-Teichmann, 1998). Retinal, pineal and specific deep-brain opsins, as well as several molecules of the phototransduction cascade have been demonstrated in septal and anterior hypothalamic CSF-contacting neurons of various vertebrates. As the corresponding areas are known to play a role in breeding behaviour, a relationship between the deep brain photoreceptors and photoperiodic gonadal response has been suggested (Foster et al., 1994; Garcia-Fernandez et al., 1994, 1997; Grace et al., 1996; Wada et al., 1998).

CSF-contacting neurons are also present among secondary neurons of the pineal organ. Moreover, retinal bipolar cells that send a dendrite into the photoreceptor space of the retina and form there the so-called Landolt clubs, are cytologically similar to CSF-contacting neurons (Vígh et al., 1983; Vígh and Vígh-Teichmann, 1988). Retinal and pineal photoreceptors themselves develop from bipolar neuroblasts in the wall of the optic ventricle and the pineal recess, respectively, and send a dendrite to the CSF; they seem to belong to the same cell type as CSF-contacting neurons (Fig. 10). The lateral eye retina, pineal organs as well as hypothalamic CSF-contacting neurons are all constituents of the diencephalon (Vígh and Vígh-Teichmann, 1974, 1975, 1988, 1999; Vígh et al., 2001), a part of the brain that can be regarded as predominantly visual in function ("photo-encephalon").

When comparing visual and deep encephalic photoreceptors, the question arises as to whether CSF-contacting neurons lacking outer segments can function as photoreceptors. Rods and cones of the lateral eye exhibit a well developed outer segment composed of a high number of photoreceptor disks in order to decode two-dimensional images reflected onto the retinal surface. In the nonvisual photosensory cells, however, high sesitivity reached by photoreceptor membrane multiplications are not needed, because the cells serve only as photodosimeters to detect brightness levels of the environment. Thus, it is likely that a cell without an outer segment but having a plasma membrane loaded

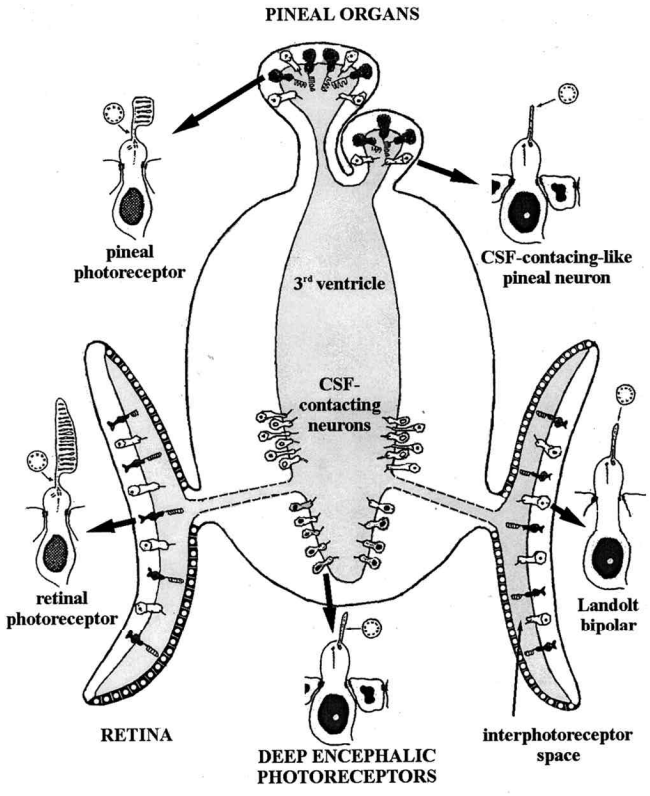

Fig. 10. Scheme on the similar periventricular origin and topography of deep brain-, pineal- and lateral-eye photoreceptors.

with opsin may operate as a photoreceptor (Fejér et al, 2001a).

Mainly called pineal "glands" in the last decades, the *pineal organs* actually represent the main nonvisual photoreceptors of vertebrates. Protruding from the brain to the surface like the lateral eye retina, besides pineal neurons and glial cells they contain photoreceptor-like pinealocytes. Pinealocytes are polarised cells, their sensory pole is marked by a 9+0-type sensory cilium developing photoreceptor lamellae in most submammalian species as well as in some mammals. The effector pole emits an axon-like process that forms synaptic contacts for neural (fast) and/or neurohormonal terminals for (slow) efferentation. The neural efferentation works with excitatory amino acids via ribbon-type synapses on secondary pineal neurons. Glutamate and aspartate also may have a role in hormonal release. The axons of secondary pineal neurons form pineal-brainstem pathways. The most intensively studied neurohormonal efferentation is the melatonin secretion. Containing, and, presumably, releasing serotonin, neurohormonal release sites do not correlate in extent with pineal melatonin secretion, they are differently developed or absent in various vertebrates (Vígh and Vígh-Teichmann, 1989b, 1999; Vígh et al., 1995a,b).

Pinealocytic outer segments express molecules of the phototransduction cascade. Being well developed in perinatal age, presumably they utilise the pineal-mediated light information in the early entrainment of rhythmic functions (Vígh and Vígh-Teichmann, 1992; Fejér et al., 2001a). Blue light-sensitive cryptochromes were localized imunocytochemically in nuclei and cytoplasmic elements of a subpopulation of pineal cells. Cryptochromes in the Drosophila participate in both the photoreception and pacemaker functions. We suggest a similar double function for cryptochromes present in the cytoplasm and cell nuclei of pinealocytes (Dávid et al., 2001).

Peripheral autonomic nerves containing different type of fibers (being presumably vasoconstrictor, vasodilator and vasosensor) reach the pineal organs. Noradrenergic fibers originating in the superior cervical ganglion were postulated to carry light information from the retina and regulate the pineal melatonin secretion in mammals. Neuroanatomically, however, it seems to be more evident that they mediate sympathetic tonus (LeGros Clark, 1940) of the hypothalamus. Daily and seasonal fluctuation of sympathetic tonus in adults may sustain pineal circadian and circannual periods entrained earlier.

Some fibers of the conarian nerve were found to terminate on smooth muscle cells of pineal precapillary arterioles. Being of the vasomotor type, these terminals cannot regulate the pinealocytes directly. Rather, they influence the pineal blood-supply, perhaps according to the different metabolic levels of the periodic pineal cell activity - as is known for the task of vasomotor fibers of other brain areas. Also, pinealopetal fibers enter the pineal via its stalk from various brainstem nuclei, e.g. from lateral geniculate nuclei, which may play a role in the interaction between retinal and pineal photoperiodic functions (Vígh and Vígh-Teichmann, 1992b; Moller et al., 1993; Fejér et al., 2001a; Vígh et al., 2001). Comparing data on pineal morphophysiology, three phases seem to exist during development of the pineal entrainment of internal pacemakers: (1) an embryologic synchronization by light, and in viviparous vertebrates, by maternal effects, (2) an early postnatal entrainment by direct photosensitivity and (3) in adults, a maintenance of periodicity by daily sympathetic rhythm of the hypothalamus.

The nonvisual photoreception of the *lateral eye* retina primarily entrains genetically-determined periodicity in ocular physiology, such as rod-cone dominance, EEG rhythms or retinomotor movements. It also influences the suprachiasmatic nucleus, the primary pacemaker of the brain. Since the known rods or cones apparently do not represent nonvisual photoreceptors in the retina, the presence of additional photoreceptors must be supposed. Cryptochrome 1 localized to a subpopulation of retinal photoreceptors may be a candidate for the nonvisual photoreceptor molecule of the retina. Immunocytochemically-localized in some cells of the inner granular layer, it may also have a role in the retinal pacemaker system (Dávid et al., 2001).

Brain areas similar to the suprachiasmatic nucleus, the "master" pacemaker of the mammalian brain, also exist in lower vertebrates (Tilgner et al., 1990). Immunoreactivity with antibodies against bovine rhodopsin, rod- and cone-transducin was detected in the suprachiasmatic nucleus in the bullfrog (Okano et al., 2000). In addition, the gene of melanopsin, the opsin of photosensitive dermal melanophores of *Xenopus laevis* was found to be transscribed in Xenopus tadpoles in the suprachiasmatic nucleus (Provencio et al., 1998). These results suggest, that the principal suprachiasmatic circadian pacemaker of higher vertebrates may be derived from deep encephalic photoreceptors of lower vertebrates.

In addition to nonvisual and visual photoreception, the existence of a transitory, *"semivisual"* light-perceptive function was supposed for some deep brain photoreceptors and pineal organs. The spinal photoreceptors of the lancelet, the pineal organ of cyclostomes and some fishes, the extracranial frontal eye of anurans, and the parietal eye of reptiles may possess some directional light perception aided by skull windows, lens-like structures, light conducting "pineal apparatus", and reflecting crystals or shadowing pigment cells. This directional photoreception is supposed to serve negative phototaxis in aquatic animals like the lancelet, or support thermoregulation by detecting places of direct solar irradiation for poikilotermic terrestrial species, like lacertilians (Hartwig and van Veen, 1979; Hartwig and Oksche, 1982; Underwood and Gross, 1982, Vígh and Vígh-Teichman, 1988; Foster et al., 1993).

Concerning *phylogenetic aspects of photoreception*, we have to emphasise that the prochordate lancelet only have nonvisual and semivisual encephalic photoreceptors. In the roof of the lancelet "brain", ciliated and rhabdomic photoreceptor cells are present (Satir cells and Joseph cells). Similarly to retinal and pineal photoreceptors, the Satir cells develop photoreceptor outer segments from a ciliary membrane, therefore they may be regarded as "precursors" of vertebrate photoreceptors (Eakin and Westfall, 1962; Eakin, 1968; Barnes, 1971; Watanabe and Yoshida, 1986; Ruiz and Anadon, 1991a,b; Vígh and Vígh-Teichmann 1999). As the lancelet does not have a lateral eye, we can suppose that nonvisual photoreception preceedes the visual one in vertebrate evolution. A part of the ancestral deep brain photoreceptors could be evolved into nonvisual pineal, some of them into semivisual- and finally, into visual photoreceptors (Vígh-Teichmann et al., 1980a; Vígh and Vígh-Teichmann, 1982; Vígh-Teichmann and Vígh, 1983, 1999; Vígh et al., 2001). Being in accord with the theory of common origin of photoreceptors, pineal and retinal opsins were traced phylogenetically back to a single common ancestor (Yokoyama, 1996).

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