mammals have apparently lost the ability to perceive light extraretinally.

The localization of EOP's in invertebrates may not be so surprising in view of the fact that the central control of circadian rhythms and photoperiodic time measurement in molluscs and insects is also mediated by brain structures. In vertebrates, this correspondence between the site of the brain photoreceptors and the central neural mechanisms controlling these two functions is even more conspicuous. The pineal system, itself a photoreceptive structure, has been identified as an important component of the circadian pacemaker in lower vertebrates and birds[8]. The ventral diencephalon, moreover, contains the suprachiasmatic nuclei which are regarded as a putative circadian pacemaker in birds and mammals. Pinealectomy and lesions of the suprachiasmatic nuclei also abolish the animal's ability to respond to changing photoperiod[8]. Thus there seems to be a close structural relationship between EOP's and those regions of the diencephalon which utilize their photosensory capacity to respond to the daily illumination cycle and the seasonal lengthening and shortening of the photoperiod.

EOP's also present us with problems relating to the mechanisms of phototransduction and their morphological and anatomical organization. Unfortunately comparatively little is known about these more microscopic questions. In two cases, however, a detailed study at the cellular level has recently become possible: the photoreceptive neurones of the abdominal ganglion of *Aplysia* and the pineal and parietal organs of lower vertebrates. Here the photoreceptors are identified and can therefore be subjected to the full range of experimental techniques available to the photobiologist. In this way many details of the photochemistry and electrophysiology of these cells have been unravelled. In those instances where localization has as yet proved impossible, progress is being made with the microphotospectrometric analysis of tiny sections of brain tissue containing photoreceptor cells.

In the following papers many of the different aspects of EOP will be reviewed. The electrophysiological and photobiological study of 3 types of identified EOP's is discussed in the first three contributions. Andresen and Brown will summarize their work on the photosensitive neurones in the molluscan brain and demonstrate how nerve cells lacking the classical morphology of ocular photoreceptors transduce photic energy into a conductance change of their membrane. In the second and third papers the visual properties of diencephalic photoreceptors in the vertebrate brain are described by Hartwig and Oksche, while Dodt and Meissl review the neurobiology of another identified extraocular photoreceptive system in vertebrates: the pineal and parietal organs. The last three papers focus on the functional aspects of EOPs. Here their localization and function are reviewed for the invertebrates by Page and for the vertebrates by Underwood and Groos. In these two papers separate attention will be given to the importance of EOPs relative to that of the eyes. In the last review by Oliver and Baylé the special case of encephalic photoreception in birds will be discussed in detail.

The present review series demonstrates the functional significance of extraocular photoreception for a wide variety of species in which EOP's have been described. No doubt neurobiologists will direct increasing attention on extraocular photoreception extending our modest understanding presently reflected in this review series.

1 G.A. Russell, Ibn al-Haytham – the first biophysicist. TINS *2*, VIII–XI (1979).
2 K. von Frisch, Beiträge zur Physiologie der Pigmentzellen in der Fischhaut. Pflügers Arch. *138*, 319-387 (1911).
3 G.H. Parker, The skin and eyes as receptive organs in the reaction of frogs to light. Am. J. Physiol. *10*, 28-36 (1903).
4 A.S. Pearse, The reactions of amphibians to light, Proc. Am. Acad. Arts Sci. *45*, 161-208 (1910).
5 B.K. Follett, ed., Biological clocks in reproductive cycles. John Wright, Bristol 1981.
6 J. Aschoff, ed., Handbook of behavioural neurobiology, vol. 4, Biological rhythms. Plenum Press, New York-London 1981.
7 J. Benoit, The structural component of the hypothalamo-hypophyseal pathway, with particular reference to photostimulation of the gonads in birds. Ann. N.Y. Acad. Sci. *117*, 23-34 (1964).
8 B. Rusak and I. Zucker, Neural regulation of circadian rhythms. Physiol. Rev. *59*, 449-526 (1979).

Neurobiological aspects of extraretinal photoreceptive systems: structure and function*

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In vertebrates, photosensory systems that in part have been proven to mediate environmental photoperiodic cues synchronizing self-sustaining clock mechanisms have evolved from the matrix of the diencephalon along 3 different lines: a) lateral eyes and their retinohypothalamic projections, b) deep encephalic photoreceptors, and c) pineal sense organs (for references see Oksche and Hartwig[1]). In mammals, retinohypothalamic projections to the suprachiasmatic nucleus appear to be a sufficient photosensory input channel entraining autonomous rhythmic events with an external light regimen (for review, see Rusak and Zucker[2]).

Various avian species possess an encephalic photosensory apparatus in the hypothalamus controlling the photoperiodic induction of gonadal growth and regression (for review, see Yokoyama et al.[3]). However, retinal photoreceptors appear to contribute to the entrainment of circadian systems (Menaker and Underwood[4]).

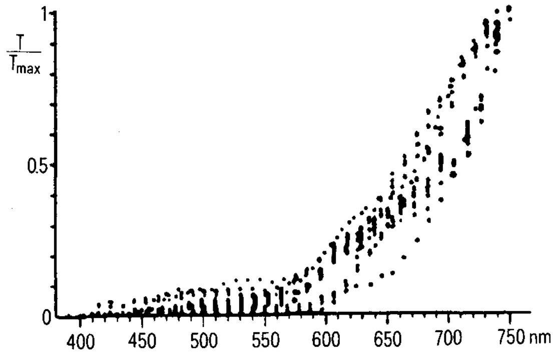
In poikilothermic vertebrates the interaction between retinal, pineal and encephalic photosensory mechanisms in the control of circadian and circannual mechanisms has not been investigated in detail. In some species it has been shown that under experimental conditions the entrainment of endogenous rhythms can be mediated by extraretinal and extrapineal photoreception (for review of findings in reptiles and amphibians, see Adler[5], Rusak and Zucker[2]; for recent observations in reptiles, see Kavaliers[6]; for evidence in teleost fishes, see Kavaliers[7]; van Veen et al.[8]).

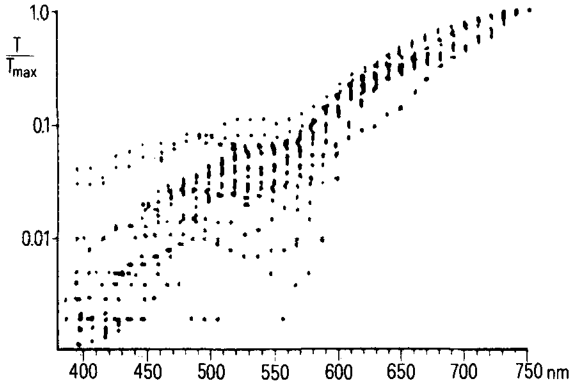
In summary, it has been repeatedly proven that vertebrates, with the apparent exception of mammals, possess encephalic photoreceptive areas. Most probably these enigmatic photoreceptors are located in the vicinity of the wall of the third ventricle (Oksche and Hartwig[1,9]; for general review of extraocular photosensitivity in vertebrates and invertebrates, see Wolken and Mogus[10]). In the following survey attention will be focussed on attempts to identify those brain regions that may have provided the receptor for light-dependent entrainment of rhythmic functions prior to the evolution of the lateral eyes (Underwood[11]).

The first report dealing with the observation of extraretinal and extrapineal photoreception was published by Karl von Frisch[12] in 1911: illumination of the diencephalon of blinded and pinealectomized European minnows, *Phoxinus phoxinus*, resulted in color change of the skin. In the same species Scharrer[13] was able to show that encephalic photoreceptors can mediate light-dependent conditioned reflexes. Van Veen et al.[8] reported that in blinded and pinealectomized European eels, *Anguilla anguilla*, encephalic photoreceptors are responsible for the synchronization of the circadian changes in motor activity with an external photoperiod as well as for the control of photonegative behavior. Recently, van Veen[18] in threshold experiments presented evidence that entrainment of (circadian) motor activity in intact, blinded, and blinded + pinealectomized European eels is established by equal amounts of light. Consequently, the question arises whether the eyes and/or the pineal complex are a substantial prerequisite for the light-dependent entrainment in intact eels. Light entraining autonomic rhythmic functions via extraocular and extrapineal photoreceptors must penetrate the skin and its derivatives, the bony skull, meningeal tissues, blood vessels and brain tissues before reaching its target. In man and mammals it has been shown that the visible radiation of the solar illumination can penetrate into nearly all compartments of the body including the hypothalamus (for review, Wurtman[14]). The penetrating radiation is scattered and its spectral composition is modified by a color-filter effect of substances absorbing wavelengths in the visible range of the spectrum (e.g., hemoglobin and melanin). Van Brunt et al.[15] observed that in mammals the absolute amount of light reaching the brain is inversely proportional to the size of the animal investigated. This has been confirmed by Hartwig and van Veen[16] in spectral transmission recordings (ranging from 400 to 750 nm) conducted in 2 species of teleosts *(Anguilla anguilla, Ictalurus nebulosus)*, an amphibian *(Rana temporaria)*, a reptile *(Lacerta muralis)*, and 2 species of birds *(Passer domesticus, Columbia livia)*. These authors found that in all species investigated visible radiation of longer wavelengths (700-750 nm) penetrated 100-1000 times more effectively than that of shorter wavelengths (400-450 nm). The slope of the transmission curve resembled that of a barrier filter (cut-on type) with the typical wavelength (= 50% transmission) between 650 and 700 nm. However, the steep decrease of transmission values characteristic of barrier filters is interrupted between wavelengths from 500 to 540 nm. This small plateau in the slope of the transmission curve apparently depends on the transmission characteristics of hemoglobin present in the red blood cells of the vascular system (figs 1,2). Considering these data it can be expected that at least in large animals possessing encephalic photoreceptors the maximal sensitivity might be expected to occur in the range of long wavelengths.

There exists only a limited number of experiments dealing with the spectral response of encephalic photoreceptors. Benoit[17] reported that after blinding of large birds, i.e. the duck, photoperiodically induced testicular growth showed its highest rate after illumination of the hypothalamus with long wavelengths (600-650 nm). However, van Veen and Anderson (see van Veen[18]) who investigated smaller vertebrates, European yellow eels, obtained different results. In blinded and pinealectomized specimens long wavelengths (665-700 nm) failed to entrain circadian locomotor rhythms via extraretinal and extrapineal photoreceptors at energy levels adjusted to an equal number of photons reaching the diencephalon, whereas synchronization did take place when the photoperiod consisted of wavelengths of $\lambda = 447$, 497, or 548 nm ($\Delta\lambda = 16$ nm).

Menaker and coworkers (McMillan et al.[19]) showed that in the house sparrow electromagnetic radiation between 600 and 700 nm characterized by an energy of only 0.15 $\text{erg} \cdot \text{cm}^{-2} \cdot \text{sec}^{-1}$ measured at the head surface of the animal is capable of penetrating the tissues covering the encephalic photoreceptors and stimulating photoperiodically induced gonadal growth. In terms of W per cm^2 ($1\ \text{W} = 10^7\ \text{erg} \cdot \text{sec}^{-1}$) this is roughly a radiant energy of $10^{-8}\ \text{W} \cdot \text{cm}^{-2}$. From the data published by Hartwig and van Veen[16] it can be computed that at 650 nm the absolute values of transmission of tissues covering the hypothalamus are $T_{650\,\text{nm}} = 0.1 - 10 \times 10^{-5}$. Consequently, a radiant energy between $0.1 - 10 \times 10^{-13}\ \text{W} \cdot \text{cm}^{-2}$ or $0.1 - 10 \times 10^{-7}\ \mu\text{W} \cdot \text{cm}^{-2}$ between 600 and 700 nm present at the level of the hypothalamus is sufficient to be recorded by encephalic photoreceptors. This value is in the range of the threshold for photomorphogenesis in plants (bean hypocotyl; red-light exposure) and in the range of the threshold of the electrophysiological response in the dark-adapted retina of the cat (15-sec exposure; for details and references, see Seliger and McElroy[20]).





Figures 1 and 2. Spectral transmission recordings of light penetrating into the hypothalamus. Each dot represents 1 single measurement. The figures show corrected instrument readings expressed as T (transmission) divided by T_{max} (maximal transmission value). The data obtained in teleosts, amphibians, and birds (Hartwig and van Veen[16]) have been combined into single diagrams by photomechanical techniques. Transmission values are plotted in a linear (fig. 1) or a log scale (fig. 2) against wavelength (nm). Absolute values of transmission at 670 nm: *Anguilla anguilla* and *Ictalurus nebulosus* approximately $4 \cdot 10^{-5}$, *Rana temporaria* approximately 0.01; *Passer domesticus* approximately 1.5×10^{-6}; *Columba livia* approximately 1.2×10^{-7}.

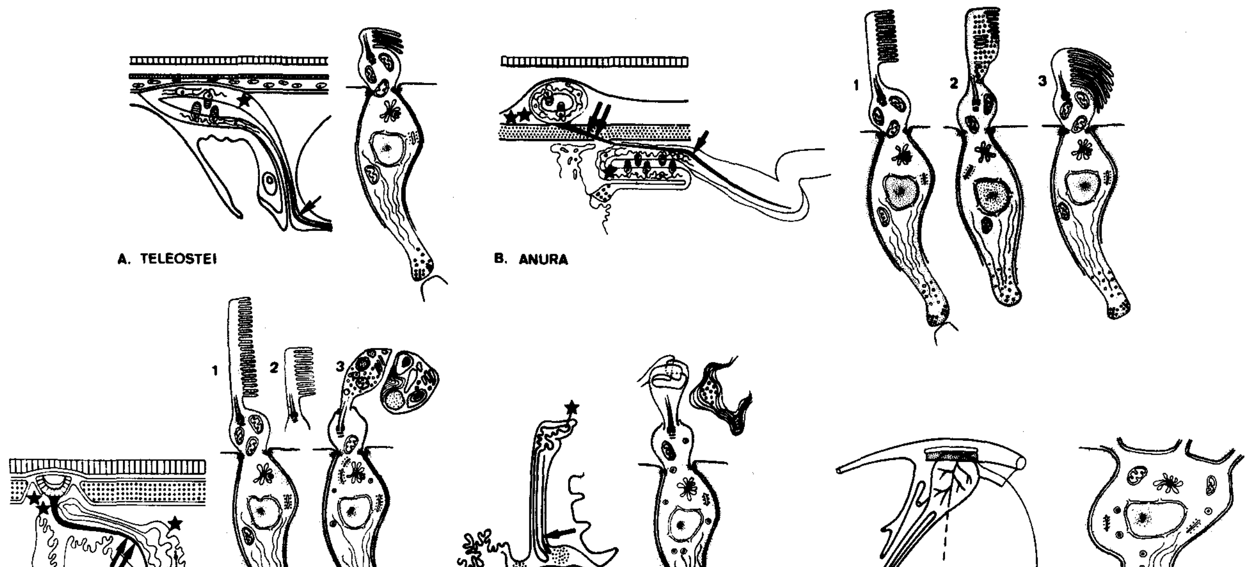
Considering that retinal and pineal photosensory systems derived from the matrix of the diencephalon possess membrane-bound photopigments responsible for the primary process of photoreception, one can assume that the enigmatic encephalic photoreceptors also contain photopigments. Furthermore, the high sensitivity of the encephalic photoreceptive systems can only be achieved by an integrating apparatus of neurons. It is astonishing that various attempts to locate encephalic photosensory elements and their integrating neuronal apparatus by morphological techniques have only been partially successful (cf. Hartwig[21]). In small individuals of *Phoxinus phoxinus* and *Carassius auratus* (body lengths: 2-4 cm) and in tadpoles of *Rana temporaria,* Hartwig[21] (see also Oksche and Hartwig[1]) using microspectrophotometric techniques detected, in 30-50-μm-thick frozen sections, a circumscribed ependymal area covering the antero-dorsal hypothalamus that contained a photolabile compound. This substance exhibited an ill-defined absorption maximum between 560 and 580 nm and a specific density at λ_{max} of 0.0004-0.0013/μm. The optical density at λ_{max} for photopigments in outer segments of retinal and pineal photoreceptors is in the range of $0.013 \pm 0.002/\mu\text{m}$ (for retinal photoreceptors, Liebman[22]; for pineal photoreceptors, Hartwig and Baumann[23]; Hartwig[21]; Oksche and Hartwig[1]). Comparing the optical density found in retinal and pineal photoreceptor outer segments with that of the photolabile compound observed in the wall of the third ventricle, one has to consider that in regularly lamellated outer segments of photoreceptor cells more than 50% of the dry weight consist of photopigment molecules. Since regularly lamellated structures have not been observed in areas containing the photolabile compound, the question arises whether this substance is indeed a photopigment. An alternative would be that the observed light-dependent changes of absorption values in the vicinity of the third ventricle reflect light-dependent changes of absorption values (interpreted as photodecomposition of a photosensitive compound) at concentrations of certain compounds playing an active role in the intermediate metabolism (e.g., cytochromes, riboflavins). It must be pointed out that the light-dependent change of transmission values was exclusively restricted to the above-mentioned areas. From a comparative point of view, these regions do not correspond to the photosensitive area found in the hypothalamus of the white-crowned sparrow, *Zonotrichia leucophrys gambelii,* by means of experimental local illumination via implanted small-diameter optic fibers (Yokoyama et al.[3]). The region identified microspectrophotometrically is located in the area of the diencephalon that has been shown to be engaged in the control of light-dependent conditioned reflexes in blinded and pinealectomized European minnows (Scharrer[13]). In this context it is important to note that there is experimental evidence that in the house sparrow circadian and circannual photoperiodic systems might be entrained by different types of extraretinal photosensory mechanisms (for review, Menaker and Underwood[4]).

At the electron-microscopic level, the area of the teleost brain that has been shown to contain a photolabile compound displays cells contacting the cerebrospinal fluid with bulbous cilia of the sensory type ($9\times2+0$); these cells resemble early developmental stages of retinal and pineal photoreceptor outer segments, or - in some respects - cerebrospinal fluid-contacting neurons. However, structures rich in mitochondria that may correspond to inner segments have not been found in association with the bulbous cilia (cf. Oksche and Hartwig[9]).

In microspectrophotometric recordings conducted on frozen sections from the diencephalon of the house sparrow obtained under various experimental conditions there was no evidence for the presence of a photolabile compound (Hartwig[21]). Furthermore, in large-sized individuals of *Phoxinus phoxinus* (body length 10-14 cm) attempts to record a photolabile compound in the vicinity of the third ventricle have been unsuccessful (Hartwig[21]).

In vertebrates, photoreceptor cells bearing lamellated outer segments have been found only in the retina and in the pineal complex of fish, amphibians and lacertilian reptiles (figs 3,4). Retina and epiphysis cerebri have developed as ventrolateral and dorsal evaginations of the diencephalon, respectively. Apparently a circumscribed area of the diencephalic primordium is the only region in the central nervous system of vertebrates capable of forming photoreceptor cells. In this respect it is interesting to note that Sacerdote[24] observed differentiations of ectopic retinal structures in the mediobasal hypothalamus in *Triturus cristatus* bearing a methylene blue-stained barrier that interrupted the hypothalamo-hypophyseal tract.

Photoreceptor cells characterized by regularly lamellated outer segments exist only in connection with specialized supporting elements (e.g., pigment epithelium, Hollyfield and Witkovsky[25]). Regularly lamellated outer segments are mandatory for a high optical density of the membrane-bound photopigments necessary in circumscribed compartments serving an image-analyzing function. The encephalic photoreceptors detect the luminous flux reaching the dience-



A. TELEOSTEI B. ANURA C. LACERTILIA D. AVES E. MAMMALIA

Figure 3. Comparative anatomy of pineal complexes (derivatives of pineal and parapineal primordia). Diagrammatic midsagittal sections in relation to the characteristic cells of the sensory line. *A* Teleostei: *, pineal organ; →, pineal tract. Outer segment of the receptor cell relatively short and mostly overlapping the inner segment. *B* Anura: **, frontal organ; ⇉ frontal-organ nerve; * epiphysis cerebri; → pineal tract. Outer segments (1) regular (conelike), (2) irregular (vesiculated), or (3) domelike. Occasional rudimentary (bulbous) outer segments. *C* Lacertilia: ** parietal eye (apparently derivative of the parapineal primordium); ⇉ parietal nerve; * epiphysis cerebri; → pineal tract. Parietal eye: long, regular outer segments, (1); epiphysis cerebri: short regular outer segments (2), irregular forms (3), and bulbous cilia characteristic of rudimentary photoreceptor cells. The latter contain numerous dense-cored vesicles and do not form typical synapses with secondary neurons. *D* Aves: → pineal tract. Avian pinealocytes belong to the type of rudimentary photoreceptor cells. *E* Mammalia: Pinealocytes of adult mammals are secretory cells devoid of outer segment structures. According to Oksche (from M. Menaker and A. Oksche, Avian Biology *4*, 79-118 (1974). Courtesy Academic Press).

phalon rather than the spatial distribution of penetrating radiation. The luminous flux reaching the diencephalon is compared with the expected level indicated by the phase angle of the 'biological clock'. This can be fulfilled by membrane-bound photopigments distributed over a large area, whereas in the retina a photon reaching an outer segment must be absorbed immediately in order to attain optimal spatial resolution. In this respect the question raised by Ernst Scharrer[26] is still unsolved: Do all neurons lining the third ventricle or only specialized elements possess photosensory functions? It cannot be excluded that only a limited, although constant number of photosensory elements is required to record the light penetrating into the diencephalon. With increasing size of the brain these elements might be scattered over larger areas. This could explain the fact that microspectrophotometric recordings searching for a photolabile compound were successful only in young, small individuals.

When considering structure, function and location of encephalic photoreceptors, additional mechanisms of photosensitivity may be of importance: 1. photosensitive enzymes (Hug et al.[27]), 2. oscillatory fluctuations of enzyme activities induced by radiant energy (Comorosan et al.[28]), and 3. enzyme inhibition or activation by photochromic compounds (e.g. carotenoids, hemoproteins; Deal et al.[29]). Recently, Cremer-Bartels and Ebels[30] have shown in vitro that pteridines, products of the photolytic degradation of folic acid, may function as nonretinal regulators of light-dependent melatonin biosynthesis. This most interesting observation might explain the finding that in the cultured pineal organ of the domestic fowl the biosynthesis of biogenic monoamines can be influenced by exposure to light (Binkley et al.[31]; Takahashi et al.[32]); although, in contrast, electrophysiological investigations have failed to show a direct response of the avian pineal organ to light (cf. Oksche and Hartwig[1]).

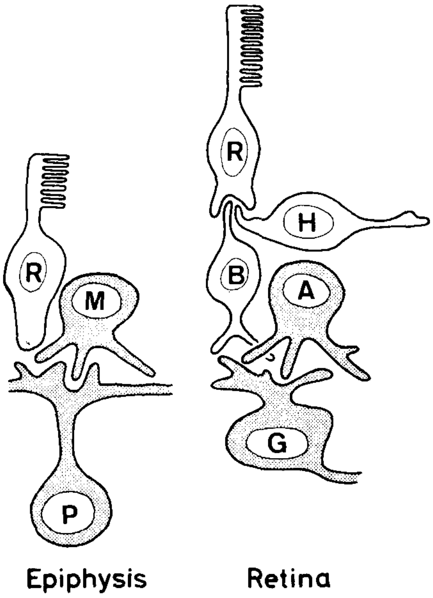


Figure 4. Neuronal organization of the pineal complex of the frog in comparison to the neuronal circuitry of the retina (basic connectivities). Epiphysis: R, photoreceptor cell; M, multipolar nerve cell (interneuron); P, neuron of the pineal tract. Retina: R, receptor cell; B, bipolar cell; H, horizontal cell; A, amacrine cell; G, ganglion cell of the optic nerve. A, G, M and P are acetylcholinesterase-positive elements (from K. Wake, M. Ueck and A. Oksche, Cell Tissue Res. *154*, 423-442 (1974). Courtesy Springer-Verlag).

Note added in proof:

For recent findings dealing with light-dependent uptake and retention of tritiated deoxyglucose by a circumscribed area of the wall of the third ventricle in in vitro-experiments see the following reference: H.G. Hartwig, Retinale und extraretinale Photorezeptoren: Messfühler und Integratoren der 'Biologischen Uhr'. Verh. anat. Ges. *77*, in press (1982).

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1 A. Oksche and H.-G. Hartwig, Pineal sense organs - components of photoneuroendocrine systems. Progr. Brain Res. *52*, 113-130 (1979).

2 B. Rusak and I. Zucker, Neural regulation of circadian rhythms. Physiol. Rev. *59*, 449-513 (1979).

3 K. Yokoyama, A. Oksche, Th.R., Darden and D.S. Farner, The sites of encephalic photoreception in photoperiodic induction of the growth of the testes in the white-crowned sparrow, *Zonotrichia leucophrys gambelii*. Cell Tissue Res. *189*, 441-467 (1978).

4 M. Menaker and H. Underwood, Extraretinal photoreception in birds. Photochem. Photobiol. *23*, 299-306 (1976).

5 K. Adler, Extraocular photoreception in amphibians. Photochem. Photobiol. *23*, 275-298 (1976).

6 M. Kavaliers, Circadian rhythm of extraretinal photosensitivity in hatchling alligators, *Alligator mississippiensis*. Photochem. Photobiol. *32*, 67-70 (1980).

7 M. Kavaliers, Retinal and extraretinal entrainment action spectra for the activity rhythms of the lake chub, *Couesius plumbeus*. Behav. neur. Biol. *30*, 56-67 (1980).

8 Th. van Veen, H.-G. Hartwig and K. Müller, Light-dependent motor activity and photonegative behavior in the eel (*Anguilla anguilla* L.). Evidence for extraretinal and extrapineal photoreception. J. comp. Physiol. *111*, 209-219 (1976).

9 A. Oksche and H.-G. Hartwig, Photoneuroendocrine systems and the third ventricle, in: Brain-endocrine interaction. II. The Ventricular System, 2nd Int. Symp. Shizuoka 1974, Eds K.M. Knigge, D.E. Scott, H. Kobayashi and S. Ishii. Karger, Basel 1975; pp. 40-53.

10 J.J. Wolken and M.A. Mogus, Extra-ocular photosensitivity. Photochem. Photobiol. *29*, 189-196 (1979).

11 H. Underwood, Retinal and extraretinal photoreceptors mediate entrainment of the circadian locomotor rhythm in lizards. J. comp. Physiol. *83*, 187-222 (1973).

12 K. von Frisch, Beiträge zur Physiologie der Pigmentzellen in der Fischhaut. Pflügers Arch. *138*, 319-387 (1911).

13 E. Scharrer, Die Lichtempfindlichkeit blinder Elritzen. (Untersuchungen über das Zwischenhirn der Fische). Z. vergl. Physiol. *7*, 1-38 (1928).

14 R.J. Wurtman, The effects of light on man and other mammals. A. Rev. Physiol. *37*, 467-483 (1975).

15 E.E. van Brunt, M.D. Shepherd, J.R. Wale, W.F. Ganong and M.-T. Clegg, Penetration of light into the brain of mammals. Ann. N.Y. Acad. Sci. *117*, 217-224 (1964).

16 H.-G. Hartwig and T. van Veen, Spectral characteristics of visible radiation penetrating into the brain and stimulating extraretinal photoreceptors. J. comp. Physiol. *130*, 277-282 (1979).

17 J. Benoit, The structural components of the hypothalamo-hypophyseal pathway, with particular reference to photostimulation of the gonads in birds. Ann. N.Y. Acad. Sci. *117,* 23-34 (1964).

18 Th. van Veen, A study on the basis for Zeitgeber entrainment with special reference to extra-retinal photoreception in the eel. Thesis, Department of Zoology, University of Lund, Lund, Sweden, 1981.

19 J.P. McMillan, H.A. Underwood, J.Y. Elliot, M.H. Stetson and M. Menaker, Extraretinal light perception in the sparrow. 4. Further evidence that the eyes do not participate in photoperiodic photoreception. J. comp. Physiol. *97,* 205-214 (1975).

20 H.H. Seliger and W.D. McElroy, eds, Light: physical and biological action. Academic Press, New York/London 1965.

21 H.-G. Hartwig, Neurobiologische Studien an photoneuroendokrinen Systemen. Habilitationsschrift im Bereich Humanmedizin der Justus Liebig-Universität, Giessen 1975.

22 P.A. Liebman, Microspectrophotometry of photoreceptors, in: Handbook of Sensory Physiology Vol. VII/a. Photochemistry of Vision, pp. 417-480. Eds J.A. Herbert and Dartnall. Springer, Berlin/Heidelberg/New York 1972.

23 H.-G. Hartwig and Ch. Baumann, Evidence for photosensitive pigments in the pineal complex of the frog. Vision Res. *14,* 597-598 (1974).

24 M. Sacerdote, Differentiation of ectopic retinal structures in the hypothalamo-hypophysial area in the adult crested newt bearing a permanent hypothalamic lesion. Z. Anat. Entwicklungsgesch. *134,* 49-60 (1971).

25 J.G. Hollyfield and P. Witkovsky, Pigment retinal epithelium involvement in photoreceptor development and function. J. exp. Zool. *189,* 357-377 (1974).

26 E. Scharrer, Photo-neuro-endocrine systems: General concepts. Ann. N.Y. Acad. Sci. *117,* 13-22 (1964).

27 D.H. Hug, D. Roth and J.K. Hunter, Photoactivation of an enzyme and biological photoreception: a hypothesis. Physiol. Phys. *3,* 353-360 (1971).

28 S. Comorosan, D. Sandru and E. Alexandrescu, Oscillatory behaviour on enzyme reactions: a new phenomenon. Enzymologia *38,* 317-328 (1969).

29 W.J. Deal, B.F. Erlanger and D. Nachmansohn, Photoregulation of biological activity by photochromic reagents. III. Photoregulation of bioelectricity by acetylcholine receptor inhibitors. Proc. natl Acad. Sci. *64,* 1230-1234 (1969).

30 G. Cremer-Bartels and I. Ebels, Pteridines as nonretinal regulators of light-dependent melatonin biosynthesis. Proc. natl Acad. Sci. *77,* 2415-2418 (1980).

31 A. Binkley, J.B. Riebman and K.B. Reilly, The pineal gland: A biological clock in vitro. Science *202,* 1198-1201 (1978).

32 J.S. Takahashi, H. Hamm and M. Menaker, Circadian rhythms of melatonin release from individual superfused chicken pineal glands in vitro. Proc. natl Acad. Sci. *77,* 2319-2322 (1980).

The pineal and parietal organs of lower vertebrates

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In addition to deep encephalic photoreceptive areas, the principal site of extraocular photoreception in lower vertebrates seems to be the pineal complex. During phylogenetic development the morphological appearance of the pineal complex reveales striking differences among different species. A remarkable phenomenon is the continuous change from a photoreceptor organ to an indirectly photosensitive secretory organ with a transformation from a photoreceptor cell type (in lower vertebrates) to the secretory pinealocyte (in mammals). The great diversity in the anatomical and ultrastructural appearance of the pineal system is also reflected by the great number of functions in which it has been implicated. These include bodily changes as skin pigmentation, phototaxis, orientation, locomotion, metabolic and thermoregulatory responses and other rhythmical events which were attributed to the pineal. The present review compares the physiological performance of the pineal system of lower vertebrates in regard to their photoreceptive capacities.

Structural outline

Almost all vertebrates possess an intracranially located pineal organ, synonymously called the pineal gland or epiphysis cerebri. An extracranial part - the frontal organ (Stirnorgan), the parietal organ, or parietal eye - is found in anurans and in lizards. The frontal (parietal) organ is connected to the epiphysis by the frontal (parietal) organ nerve; a pineal tract projects from the epiphysis to other brain structures. Nerve fibers from the frontal organ were shown to form only a small part of the pineal tract[1-3]. Ultrastructurally, the pineal complex contains photoreceptive sensory cells resembling the retinal cones of the lateral eye[4-7], showing multiple membrane invaginations of their outer segments. They are shorter in length and contain a smaller number of discs compared to retinal photoreceptors[8]. The outer segments display a scattered arrangement and protrude into the pineal lumen, which communicates with the cerebrospinal fluid of the third ventricle. The majority of the receptor outer segments project in horizontal direction, arranged parallel to the roof of the bony skull[9,10].

Other cellular elements of the pineal system are nerve cells and interstitial (supportive or glia) cells. Two types of nerve cells were identified by means of the acetylcholinesterase (AChE) reaction in the pineal complex of anurans: multipolar cells - possibly interneurons - and pseudounipolar cells sending their axons into the pineal tract[11]. AChE preparations do not provide evidence for the presence of horizontal and bipolar cells in the frog's pineal organ. The amacrine-like multipolar cells of the pineal organ