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Pineal photosensitivity. A comparison with retinal photoreception

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Abstract. Pineal photoreceptors of poikilothermic vertebrates posses numerous anatomical, physiological and biochemical similarities to retinal photoreceptors, including the rhythmic melatonin biosynthesis, with nocturnal peaks and low day-time levels. This brief outline will survey the photoreceptor properties of the pineal organ of poikilothermic vertebrates, which suggest that the pineal is not only a simple light detector (that acts as a kind of photometer), but that it is capable of processing the light information and to discriminate it from informations that have no meaning for its assumed photoperiodic function.

Key words: pineal organ, photoreception, poikilothermic vertebrates, circadian rhythms, melatonin

INTRODUCTION

Rhythmic biochemical, physiological and behavioural events are controlled for the most part by the photic environment, especially by the daily alternations between day and night - the most evident periodic phenomenon of the environment. Light as the dominating synchronizing factor is perceived by ocular and extraocular photoreceptors and exerts its influence on the "biological clock" by neuronal and neuroendocrine mechanisms. The pineal organ as an important component of this biological clock is a part of photoneuroendocrine systems and is involved in the control of autonomic functions in response to changes in the photoperiodic environment (Scharrer 1964). The most obvious changes in pineal function are the rhythmic production and secretion of melatonin with a nocturnal peak and low day-time levels (cf. Yu and Reiter 1993). This characteristic release pattern is observed in all vertebrates investigated thus far, despite the fact that the pineal has undergone remarkable morphological transformations during phylogeny. Melatonin is thus considered as the neuroendocrine message indicating darkness for the organism. The circadian rhythm of melatonin production is primarily regulated by distinct daily changes in the activity of serotonin-N-acetyltransferase (NAT), the key enzyme in melatonin biosynthesis, that converts serotonin to N-acetylserotonin. A second enzyme, hydroxyindole-O-methyltransferase (HIOMT) methylates N-acetylserotonin to melatonin. Besides this melatonin pathway, numerous methoxyindoles and hydroxyindoles are also synthesized in the pineal organ (for review see Yu and Reiter 1993).

The activity of NAT, the rate-limiting enzyme in biosynthesis of melatonin is controlled by the light environment. Acute light exposure in the night dramatically suppresses the nocturnal increase of NAT activity and melatonin production. According to the current assumptions melatonin is not stored in the pineal parenchmya, but is released directly into the general circulation immediately after its formation (Reiter 1991). Thus, melatonin release from the pineal organ reflects directly its synthesis.

The light-dependent melatonin signal is highly conserved throughout all vertebrate classes, but its control by light has undergone remarkable transformations during the process of phylogeny (cf. Collin 1971, Oksche 1971). In higher vertebrates, a photic influence on pineal function is mediated by photoreceptors of the retina and a complex neural pathway with projections of the retinohypothalamic tract to the suprachiasmatic nucleus (SCN), the major oscillator in the mammalian brain, and via the upper thoracic spinal cord to the superior cervical ganglion whose post-ganglionic sympathetic fibers innervate the pineal organ (Moore 1978). In mammals the sympathetic innervation is required for maintaining the light influence on melatonin synthesis. However, modern tracing studies have provided evidence that the mammalian pineal gland is also innervated by fibers of central origin (Møller and Korf 1983, Korf and Møller 1984). This central innervation obviously transmits photic information from the retina to the pineal gland as was shown by electrophysiological recordings (Dafny 1980, Thiele and Meissl 1986, Martin and Meissl 1990) and modulates nocturnal pineal indole metabolism (Møller et al. 1987).

In poikilothermic vertebrates light acts directly on the pineal organ without the involvement of the retina (cf. Dodt 1973, Meissl and Dodt 1981, Meissl 1986). This direct photosensitivity is provided by true photoreceptor cells that resemble retinal rods and cones (cf. Table I). They are endowed with outer segments which protrude into the pineal lumen and consist of numerous discs (cf. Vollrath 1981) and they contain photopigments and proteins that are known to be involved in the retinal phototransduction process (cf. van Veen et al. 1986, Korf et al. 1986, Korf et al. 1992). These typical pineal photoreceptors are, according to the concept of the receptor cell line, the phylogenetic precursors of modified photoreceptors found in sauropsidians and of mammalian pinealocytes (Collin 1971, Oksche 1971). Distinct interspecies differences exist not only with respect to the morphological appearance of pinealocytes, but also in the neuronal organization of the pineal.

DIRECT PHOTORECEPTION IS A PECULIARITY OF THE PINEAL COMPLEX OF POIKILOTHERMIC VERTEBRATES

In poikilothermic vertebrates, pineal photoreceptors receive the environmental photic information directly without the involvement of the retina of the lateral eyes and transmit the processed light information to various brain areas by modulating the impulse frequency of second order neurones and also by modulation of the endocrine melatonin signal. In response to brief light flashes, the basic pattern of pineal photoreceptor responses is, similarly to retinal receptors, a hyperpolarizing response starting from a resting potential between -25 mV and -35 mV (Meissl and Ekström 1988a), i.e. photoreceptors are partly depolarized in darkness. A fundamental property of photoreceptors is the increase of response amplitude with increasing flash intensity in a restricted range. The relation between amplitude and intensity can be described by a hyperbolic tangent function, a modified form of the Michaelis-Menten equation, which was first used by Naka and Rushton to describe the behaviour of retinal horizontal cells to increasing intensities of

TABLE I

Comparison between structure and physiological properties of pineal and retina

	Pineal	Retina
Position	intracranial, but some species possess an extracranial parietal eye or frontal organ	superficial
Optic media	opaque to transparent	clear
Photoreceptor structure	cone-like (some rod-like) with small or rudimentary outer segments	cones and rods with well-developed outer segments
Outer segments	<50 disks	>1000 disks (*rods*)
Second-order neurons	projecting neurones (ganglion cells) and possibly a small population of interneurons	horizontal, bipolar, amacrine and ganglion cells with several cell populations
Cellular organization	no apparent stratification	organization into 3 nuclear and 2 plexiform layers
Photoreceptor potentials	hyperpolarization, some with depolarization	hyperpolarization
Time course	low temporal resolution, slow time course	high temporal resolution, fast response, short integration times (*cones*) low temporal resolution, slow response, longer integration times (*rods*)
Intensity-amplitude relation	similar to retinal receptors, but covering a wider range than in retinal photoreceptors	follows Naka-Rushton function
Sensitivity	high sensitivity	high sensitivity (*rods*) lower sensitivity (*cones*)
Photopigments	one or more photopigments, dependent on species	rhodopsin and several cone photopigments, dependent on species
Adaptation	adapts over a wide range of intensities, similar to retinal receptors	adapatation dependent on receptor type
Spatial resolution	no, because of the absence of a dioptric apparatus	good (*cones*)
Color vision	no, but some species show a color-dependent chromatic response	yes
Endocrine function	yes	yes (?)

light flashes (Naka and Rushton 1966). The amplitude-intensity relation of pineal photoreceptors is fundamentally similar to retinal rods and cones (cf. Table I). The experimental data can best be fitted by the equation $V/V_{max}=I^n/(I^n+\sigma^n)$, where V is the amplitude in mV, V_{max} the maximal amplitude, I the flash intensity and σ the intensity at half-saturation. The exponent n gives a measure of the inclination of the curve, i.e. the intensity range over which a photoreceptor responds to light flashes with an increase of the amplitude and is, thus, a measure for the sensitivity of a cell. The value for n is slightly lower in pineal photoreceptors compared to retinal photoreceptors. In numerous recordings from pineal photoreceptors we measured values for n between 0.65 and 1.06 in the trout (Meissl and Ekström 1988a), n = 1.0 in pineal photoreceptors of the minnow (Nakamura et al. 1986) and 0.8 in the pineal of goldfish (Meissl et al. 1986). These values correspond to those observed in photoreceptors of the lamprey pineal organ (Pu and Dowling 1981, Uchida et al. 1992). With increasing stimulus duration the exponent n shifts to somewhat smaller values leading to an enlargement of the sensitivity range (cf. Pu and Dowling 1981, Meissl and Ekström 1988b), a phenomenon that is also commonly observed in retinal receptors showing that some light adaptation occurs before the peak light response is obtained (Normann and Werblin 1974, Kleinschmidt and Dowling 1975).

However, whereas the basic response pattern of pineal photoreceptors is comparable to retinal photoreceptor potentials, they show one exception, because pineal responses exhibit a slower time course. This difference in the time course is evident when comparing the times for membrane recovery following dim flashes or the time from response onset to peak potential. Both values in pineal photoreceptors are much prolonged when compared to retinal rods and cones. The time to peak potential in pineal photoreceptors decreases from values of up to 1,200 ms for intensities near threshold, that is about 1,000 ms longer than the times observed in retinal cones of turtles (Baylor and Hodgkin 1974), to about 300 ms with saturating light flashes (Meissl and Ekström 1988a). This value is still about six times the value of retinal rod saturated responses (Cervetto et al. 1977). The time from peak to dark potential, i.e. the time for recovery of the membrane potential was also exceptionaly long for all pineal photoresponses studied so far. We observed in the trout pineal response durations of up to 60 s for bright flashes of intensity 2.5 log units above saturation with an average response duration of 25 s (Meissl and Ekström 1988a,b). From this slow time course it appears that pineal photoreceptors are highly specialized for the detection of slow, gradual changes of the surrounding intensity and cannot discriminate between rapidly changing light stimuli, a behaviour that is consistent with the present view of the pineal organ as an intermediate between the slowly changing photic environment during the day and the circadian organisation of the organism.

PINEAL PHOTORECEPTORS ALTER THEIR SENSITIVITY DURING LIGHT- AND DARK-ADAPTATION

A surprising feature of pineal photoreception is that these organs display a tremendous increase of sensitivity during dark adaptation. Earlier experiments in the pineal organ of anurans showed with extracellular recordings from pineal projecting neurones (termed in analogy to the retina as ganglion cells) that the organ possesses an extremly high light sensitivity (Dodt 1973) despite the small cross-sectional area of photoreceptor outer segments (approximately 1/10 of a retinal rod outer segment) and the relatively low number of discs. The sensitivity of the pineal organ was equivalent to threshold values measured from ganglion cells of the isolated retina of the frog (Baumann and Scheibner 1968). Because of the partly rudimentary appearance of pineal photoreceptors, it was assumed that a high convergence ratio of pineal receptors to a single ganglion cell is responsible for response amplification and the resulting high light sensitivity of

the pineal (Dodt 1966). However, the first indications that photoreceptors may be responsible for the high light sensitivity despite their, compared to retinal rods and cones, "modified" appearance, came from experiments where we recorded slow, light-evoked potentials from the pineal of anurans (Donley and Meissl 1979). These potentials, termed in analogy to the retinal electroretinogram as electropinealogram (Morita and Dodt 1973), provide a direct measure of photoreceptor activity. In these recordings we observed similar adaptational mechanisms and a similar light sensitivity as it was previously reported from ganglion cells recordings. Experiments with intracellular recordings from morphologically and electrophysiologically identified single photoreceptor cells of the isolated trout pineal proved that the high light sensitivity of the pineal is a property of the photoreceptor cell (Meissl and Ekström 1988b). The most sensitive pineal photoreceptors in the trout showed an absolute sensitivity of 270 $\mu V/photon \times \mu m^{-2}$ (Meissl 1988) and 202 $\mu V/photon \times \mu m^{-2}$, respectively (Kusmic et al. 1992) and is nearly identical to that reported for rods of the retina of Necturus (Fain and Dowling 1973).

A further similarity with retinal photoreceptors is the time course of dark adaptation following a strong bleach with an illumination of about 7 log units above dark threshold. After the bleaching illumination, the sensitivity of pineal photoreceptors is greatly diminished. Initially photoreceptor cells are maximally hyperpolarized during light exposure, but recovery of the membrane potential starts immediately after termination of the bleach and the potential slowly recovers to the previous dark potential within 2-4 min. When the photoreceptor has reached its original dark potential, sensitivity has not recovered, because the threshold as well as the voltage-intensity curves gradually shift to lower intensities and the response amplitudes to constant flashes increase. The change of these parameters in individual photoreceptor cells was observed for up to 1 hour after termination of the bleach indicating that dark adaptation proceeds during this time period. Dark adaptation curves of intracellularly recorded pineal photoreceptors, obtained with a threshold criterion, show a purely monophasic increase in sensitivity by at least 5-6 log units. The curves show an exponential time-course with a rapid sensitivity gain of up to 4 log units in the first 5 min followed by a slow phase with a further increase in sensitivity of about 2 log units (Meissl and Ekström 1988b). These data indicate that dark adaptation in pineal photoreceptors is governed to a considerable extent by photoreceptors similar to retinal photoreception.

If a dark-adapted pineal photoreceptor of the trout is exposed to stepwise increasing background illumination the photoresponses maintain the same amplitude with the exception of a small relaxation of the potential to a plateau value. This stable potential is dependent on the intensity of the background illumination and persists for the entire duration of illumination. Responses to test flashes superimposed on these backgrounds are depressed as a function of background intensity. The persistence of an intensity-related absolute value of the membrane potential during steady illumination, without showing a depolarization like retinal photoreceptors, may play a role in the regulation of melatonin secretion. Studies in photosensitive chick pineal organs show that changes in extracellular potassium concentrations affect melatonin release. Increasing potassium levels, which should depolarize the photoreceptor and should mimic dark conditions, elevates melatonin output. Thus, it was suggested that changes in the membrane potential are responsible for the regulation of melatonin output (Zatz et al. 1988). It appears that a similar mechanism may be associated with the control of melatonin secretion in photoreceptors of the pineal of lower vertebrates.

PHOTOSENSITIVE PINEAL ORGANS MAY CONTAIN SEVERAL PHOTORECEPTORS AND PHOTOPIGMENTS

The spectral sensitivities of photoreceptor cells of the pineal of poikilothermic vertebrates show

clear interspecific variations. Extracellular recordings revealed that pineal photosensitivity is often based on the presence of several photopigments which show striking similarities to the spectral sensitivity of the lateral eyes (cf. Meissl and Dodt 1981). In frogs, a spectral sensitivity was measured with extracellular recordings matching the absorption spectrum of rhodopsin in the dark adapted pineal and of an iodopsin in the light adapted state with a Purkinje-shift at the dark-night transition phase (Dodt and Morita 1964). By microspectrophotometric techniques only one photopigment was identified which maximally absorbs at 502 nm (Hartwig and Baumann 1974) like the accessory cones of the retina (Liebman and Entine 1968). A third ultraviolet-sensitive photopigment which is the basis of the color-coded chromatic response is additionally present in the pineal system of the frog (Dodt 1973). With immunocytochemistry using two polyclonal antibovine rhodopsin antibodies and a monoclonal antichicken cone-opsin antibody, four types of photoreceptor cells were distinguished in the pineal of ranid frogs (Vigh-Teichmann and Vigh 1990). Most frequently an immunoreaction against rod-opsin was detected, whereas the cone-opsin immunoreactive pineal photoreceptors are less frequent. These investigations support the view that pineal photoreceptors, similar to retinal receptors, are divided into different subpopulations containing rod- and cone-like cells. In the pineal organ of the trout, we observed with intracellular recordings spectral peak sensitivities at about 520 nm and occasionally a second photoreceptor at about 500 nm (Meissl and Ekström 1988a). These data are supported by earlier extracellular studies showing comparable action spectra (Morita 1966), but also by other intracellular recordings showing two photoreceptor populations characterized by peak sensitivities at 495 and 521 nm, respectively (Marchiafava and Kusmic 1993). However, recent microspectrophotometric measurements on isolated pineal photoreceptors of the trout revealed the existence of two photopigments with l_{max} at 463 nm and at 561 nm (Kusmic et al. 1993). The presence of two distinct visual pigments is in agreement with the electrophysiological data, but the maximal sensitivities are considerably shifted to shorter and longer wavelengths, respectively. The microspectrophotometric data differ also from the action spectrum for melatonin suppression which peaks at about 500 nm (Max and Menaker 1992). Because the electrophysiological and biochemical data were obtained from *in vitro* preparations of whole organ cultures, these differences may result from a convergence of informations from both receptor types or from neural feedback onto the photoreceptor cells. However, the presence of two different photopigments is supported by the discovery of the vitamin A_1 based chromophore, 11-cis-retinal and vitamin A_2 based 11-cis--3-dehydroretinal in the trout pineal which is similar to the retina (Tabata et al. 1985).

In conclusion, electrophysiological, biochemical, morphological and immunocytochemical studies indicate that pineal organs possess multiple photoreceptors with several photopigments which may be divided, like their retinal counterparts into rod- and cone-like populations. This raises the question of the biological significance of the presence of more than one photopigment in photosensitive pineal organs. It has been known for some time that there exists a close correlation between the visual pigments in retinal rods and cones of fishes with the spectral quality of the environmental light and the colour of the water in which they live (Lythgoe and Partridge 1989, Lythgoe et al. 1994). We believe that the multiplicity of pineal photoreceptor populations is also an expression of adaptational mechanisms to increase the sensitivity of the system to a wider spectral range than one photopigment could accomplish. Pineal photoreceptors which are primarily involved into luminance detection and not involved in spatial resolution of visual stimuli seem to integrate light over a broad range of intensities and spectral regions to regulate the synthesis and release of its hormone melatonin. The amplitude-intensity relation of pineal photoreceptors that cover a wider range than in retinal receptors, the maintanance of an intensity

related membrane potential during light exposure and the multiplicity of visual pigments seem to favor the registration of light irradiances.

In the pineal complex of many poikilothermic vertebrates a second response mechanism is occassionally observed that is clearly distinguished from the luminance response. This response type is color-coded and possesses a high sensitivity in the ultraviolet part of the spectrum (Dodt 1973, Meissl and Donley 1980). Most interestingly, this ultraviolet sensitivity, which leads to a sustained inhibition of second-order neurons, is antagonized by a long wavelengths mechanism, that is excitatory. Recently, the structural basis for this color-coded chromatic response was possibly detected by intracellular recordings from photoreceptors of an excised parietal eye (the extracranial part of the pineal system) preparation of lizards (Solessio and Engbretson 1993). In these photoreceptor cells chromatic antagonism originates in chromatically dependent depolarizing and hyperpolarizing responses of photoreceptors to light. Green light depolarizes these photoreceptors, whereas short-wavelengths antagonizes this effect. Similar responses were observed in enzymatically separated photoreceptors after removal of synaptic inputs from neighbouring cells showing that chromatic interactions reside in the same photoreceptor. The functional significance of the chromatic pineal response is probably associated with the detection of chromatic changes during twilight (Meissl 1988, Meissl and Brandstätter 1992). During dusk and dawn the spectral composition of the natural light environment shows considerable changes (cf. Munz and McFarland 1977) and may provide a very sensitive chromatic signal for the switch from an inhibitory to an excitatory neuronal activation state and *vice versa*. Thus, the chromatic response may be used to detect the beginning and end of the daily photoperiod, i.e. for detection of the beginning and end of the photoperiod. It is still unclear whether the color-coded mechanism has any effect on melatonin regulation or is only involved in the control of the neuronal output.

MELATONIN SYNTHESIS OF THE FISH PINEAL *IN VITRO* IS DIRECTLY CONTROLLED BY LIGHT

Melatonin synthesis and secretion of the pineal organ of teleosts is primarily regulated by the environmental light-dark cycle with high nocturnal secretion levels and low day-time levels (Gern and Greenhouse 1988, Falcón et al. 1992, Gern et al. 1992b). Recent evidence indicates that photoreceptors of the fish pineal, similar to mammalian pinealocytes and modified photoreceptors of the avian pineal, are the probable sites of melatonin synthesis, because these cells show a HIOMT-like immunoreactivity (Falcón et al. 1994). The eyes, which also synthesize melatonin, do not play a measurable role in the regulation of plasma melatonin titers, because blind and sighted trouts display the same responses to changes between light and darkness and to light pulses delivered during the scotophase (Gern et al. 1978, Gern and Nervina 1988). Under superfusion conditions, i.e. *in vitro*, the pineal organ of the trout responds quickly to light/dark or to dark/light changes and alters its release of melatonin and other methoxyindoles. Darkness-associated initiation of melatonin release is rapid showing significant increases in melatonin secretion within the first five minutes after the onset of darkness, whereas onset of light in dark-adapted preparations is followed by a rapid decline of melatonin release within 5-10 min (Gern et al. 1992b). Similar, but slightly longer latencies for the onset of the melatonin response were reported in the same species by Max and Menaker (1992) with approximately 15 min between the onset of light and the initiation of the response. These response latencies are approximately 10^4 times longer than for the electrophysiologically measured change of the membrane potential of retinal and pineal photoreceptors or of ganglion cells.

The light response of melatonin synthesis and release differs also in the temporal range from the electrophysiological response. In most sensory systems, the product of intensity and duration of the

stimulus is constant over a restricted range. That means for a photoreceptive system, if the intensity of a stimulating light is progressively reduced, one can increase the duration of the stimulus and still produce the same response size, i.e. the product I x t = const. (Bloch's law). This relation gives a measure for the temporal summation of a sensory system. When the duration increases beyond a certain limit, photons arrive too late to be integrated and do not contribute to the response. After this time limit, which is the critical duration over which Bloch's law applies, responses can no longer get larger, only longer, but within the time limit the photoreceptor organ is acting as a perfect mathematical integrator of the incoming light. The critical duration for most retinal visual processes is roughly 100 ms (cf. Dawson 1990). In photoreceptive pineal organs similar values were measured for the luminance response (cf. Dodt and Heerd 1962). However, the temporal summation range of the melatonin response considerably differs from this short period over which Bloch's law applies. Max and Menaker (1992) showed that the melatonin response is insensitive to photons presented in short duration stimuli, but is maximally sensitive to photons presented for more than 30 min. They estimated an integration time of approximately 45 min for this response type. However, a direct comparison of biochemical and electrophysiological data is, at present, difficult to achieve. Because of the differences in temporal summation, a dim light stimulus of several milliseconds that would be sufficient to alter photoreceptor membrane potentials and ganglion cell activity is insufficient to affect melatonin synthesis. On the other hand, irradiances presented for longer durations that are sufficient for eliciting a melatonin response would bleach the photopigments for a prolonged period, so that a long dark adaptation period is required before the electrical response recovers.

A further obstacle in the comparison of electrophysiological and biochemical data comes from the effect of temperature on the pineal response properties. Experiments on the isolated trout pineal organ that measured the light- or dark-evoked melatonin response were usually conducted at low temperatures, mostly at 9°C (Gern and Greenhouse 1988, Gern et al. 1992b, Max and Menaker 1992). At this temperature the electrophysiologically recorded light response of the pineal organ of the trout is considerably altered in comparison to higher temperatures (Tabata and Meissl 1993). Under *in vitro* conditions the optimal operating range of the pineal organ was between 15 and 20°C. At higher temperatures, neuronal activity of pineal ganglion cells was greatly diminished, but the cells were still responsive to light. At temperatures below 15°C the sensitivity to light gradually decreased and at approximately 7°C the organs became nearly completely insensitive to light. This temperature dependency may partly explain the differences between electrophysiologically and biochemically derived data on sensitivity and temporal summation of the light response.

SUMMARY AND CONCLUSION

Pineal photoreceptors of poikilothermic vertebrates possess numerous anatomical, physiological and biochemical similarities to retinal photoreceptors. The appearance of true pineal photoreceptor cells endowed with typical outer segments, the presence of photopigments and of proteins that are known to be involved in retinal phototransduction processes, and the presence of a light response that is comparable to retinal photoreceptors are the most obvious parallels. Furthermore, the pineal organ as well as the retina rhythmically synthesize melatonin with nocturnal peaks and low day-time levels and it appears that in both tissues synthesis and release are associated with the photoreceptor cell. However, while there is a fair amount known about the neurophysiological properties and melatonin formation of pineal photoreceptor cells of poikilothermic vertebrates, we know virtually nothing about the endocrine role of the pineal and how this obviously rhythmic nature of the organ may influence other rhythmic activities in lower vertebrates. Particularly in teleosts a clear demonstration of melatonin's hormonal role is for the most part lacking

(Gern et al. 1992a). Some other questions are also unsolved. For example, the physiological significance of the prominent neuronal output of the pineal of lower vertebrates is completely unknown. It appears that there exists an extensive overlapping between pinealofugal projections and primary visual centres (Ekström 1984, Yáñez et al. 1993), but its functions need to be determined. It is also not clearly understood whether the intrapineal neuronal network is involved in regulating melatonin formation and whether melatonin itself, once released, may exert local actions at target sites within the pineal comparable to its action in the retina. The role of external factors like temperature and chemical modulators on pineal function must be also considered.

This brief outline on photoreceptor properties of the pineal organ of poikilothermic vertebrates shows that the pineal is not only a simple light detector that acts as a kind of photometer, but that it is capable of processing the light information and to discriminate it from informations that have no meaning for its assumed photoperiodic function.

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