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The Pinealocyte—A Paraneuron ? A Review

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Summary. The pineal complex develops from a tubular evagination of the diencephalic roof. In amphibians a proliferation zone is the source of the pinealocytes and of the cells of the subcommissural organ. The pinealocytes are not real nerve cells, but derived likewise from the embryonic neural epithelium.

The pinealocytes of lower vertebrates are directly photosensitive; however, the morphological structures for direct light perception are gradually lost in the phylogenetic development and are absent in the pinealocytes of mammals. A secretory function is shown in the pinealocytes of all vertebrates, but it is more pronounced in the pinealocytes of reptiles, birds and mammals; dense-cored vesicles originate in the Golgi complex and are transported to and accumulated in the terminals of the basal processes near the perivascular space. Nerve cells are in synaptic ribbon contact with pinealocytes in lower vertebrates and their axons give a rise to the tractus pinealis. The nerve cells and nervous connection with the brain are absent in the pineal organ of mammals. Only few autonomic fibers reach the pineal organ of lower vertebrates, but the sympathetic and parasympathetic innervation are well developed in the pineal organ of most species of birds and mammals. The transmitter release from the sympathetic fibers is influenced by environmental light; light mediates in this way the activity of hormone producing enzymes in the pinealocytes. The synthesis of indole derivatives, like melatonin, is confirmed and the presence of a polypeptide hormone is discussed. Accordingly, the pineal organ functions as a "neuro" chemical, "neuro" endocrine transducer or photo-"neuro" endocrine organ, which converts a light input (direct in lower vertebrates, via transmitter release by sympathetic fibers in mammals) into a hormonal output. The pineal organ thus provides the animal with a "biological clock," which is geared to the lighting environment. The pineal organ is a regulator (or a regulator of regulators) for several body functions. In mammals, the influence on the synchronization of the gonadal activity is best known.

The pinealocyte is a hormone producing cell, which shows common features with the liquor contacting neurons and with the neurosecretory cells; after the definition of FUJITA (1976) the pinealocyte is said to be a paraneuron, also.

After FUJITA (1976) a paraneuron is characterized as a cell (1) whose origin is common with neurons, i.e. neuroectodermal, (2) which is able to produce substance(s) identical with or related to neurotransmitter or suspected transmitter or protein/polypeptide substance(s) which may possess hormonal actions; therefore, the cells possess synaptic vesicle-like and/or neurosecretion-like granules, and (3) which has a recepto-secretory function. It releases secretions in response to adequate stimuli acting upon its receptor site on the cell membrane.

FUJITA listed the pinealocyte as one of the paraneurons in his paper. We have

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attempted to examine in this investigation whether the pinealocyte possesses these characteristics or not.

1. Origin of the pinealocyte

Early ontogenetic studies summarized by STUDNICKA (1905), TILNEY and WARREN (1919) and BARGMANN (1943) and confirmed by KAPPERS (1960), OKSHE (1965), KELLY (1971) and CLABOUGH (1973), indicate that the pineal complex of vertebrates develops from a tubular evagination of the diencephalic roof. In the newt, a proliferation zone is the same source of new cells for the developing pineal organ and for the anterior margin of the subcommissural organ. The capacity to produce excessively large numbers of pineal cells is controlled by an influence emanating from adjacent

Fig. 1. a. Organization of the pineal complex in different vertebrate classes. *Salmo irideus*: The pinealocytes project with their inner and outer segments in inners and evers direction into the central lumen of the intracranial pineal lumen: the lumen has a connection with the third ventricle. *Rana esculenta*: The pineal complex consists of an extracranial frontal organ and an intracranial pineal organ. The axons of nerve cells in the frontal organ constitute the nervus frontalis which runs from the frontal organ to the pineal organ; these fibers intermingle with the axons of nerve cells in the pineal organ. The fibers from both organs give rise to the tractus pinealis running from the pineal organ to the brain. *Sphenodon*: The pineal complex consists of a parietal eye within the bone and an intracranial pineal organ; the nervus parietalis runs from the parietal eye to the commissura habenularum, the tractus pinealis to the commissura posterior. *Passer domesticus*; *Epimys norvegicus* (mammal): Birds and mammals possess an intracranial pineal organ only. Nerve cells and a central nervous connection between the pineal organ and the brain are absent in mammals. Figures slightly modified from STUDNICKA (1905), the mammalian pineal organ modified from KAPPERS (1960). **b.** The tractus pinealis which connects the pineal complex with the brain is well developed in lower vertebrates, reduced in some species of birds and absent in the pineal organ of mammals. The reduction of the tractus pinealis is an expression of the degree of the reduction of the sensory function in the pineal organ. The number of autonomic nerve fibers is small in lower vertebrates, it increases in the pineal organ of higher vertebrates with a pronounced secretory function of the pinealocytes. GCS indicates superior cervical ganglion.

diencephalic tissues (KELLY, 1971). KAPPERS (1971) stressed that the pinealocytes are not real nerve cells, but are derived likewise from the embryonic neural epithelium.

2. Structure and function of the pinealocyte in lower vertebrates

The organization of the pineal complex varies in form, structure and arrange-

Fig. 2. a-d. Diagrammatic illustration of pinealocytes. **a.** The wall of the pineal organ of lower vertebrates consists of pinealocytes (*P*), supporting cells (*S*) and ganglion cells (*G*). The pinealocytes consist of an outer segment, connective piece (9+0 cilium), inner segment, basal part with basal process. The inner and outer segments of the pinealocytes project into the pineal lumen; outer segments with a different size and shape are demonstrated. One nerve cell is in synaptic ribbon contact with several pinealocytes. *Cap* capillary. **b.** Conventional synapses between pineal ganglion cells (*G*) and granulated (pinealopetal, efferent) fibers are shown beside synaptic ribbon synapses between pinealocytes (*P*) and ganglion cells (*G*) (modified from VIGH-TEICHMANN et al., 1973). **c.** The pineal organ of some mammalian species, e.g. the rabbit, contains light and dark pinealocytes (*DP*). The dark pinealocytes surround the capillaries (*Cap*). The light pinealocytes contain dense-cored granules. *CJ* close junction, *RS* rosette structure, *SR* synaptic ribbon, *T* terminal of a light pinealocyte (slightly modified after ROMIJN, 1975b). **d.** Structural changes of the pinealocytes during phylogenetical development. The cone-like outer segment of lower vertebrates (left) is reduced to a modified cilium in birds and absent from the pinealocytes of mammals (right). The number of pineal ganglion cells (*G*) is high in lower vertebrates, small in birds and absent in mammals. The processes of the pinealocytes in mammals terminate on the basal lamina or penetrate into the perivascular space. The number of 40 nm vesicles decreases, the number of 100 nm granules increases in the pinealocytes from the lower vertebrates to the mammals (modified after COLLIN, 1969).

ment among different vertebrate classes (Fig. 1). Three cell types are distinguished in the pineal complex (Fig. 2 a): (1) pinealocytes which resemble photoreceptor cells; (2) supporting cells; (3) ganglion cells which are in synaptic contact with the pinealocytes; this cell type is absent in the pineal organ of mammals. The pinealocytes change in structure and function during phylogenetic development (Fig. 2 d). The differentiation of the cone-like outer segments of the sensory cells varies among vertebrate classes (Fig. 2 a, d). The epiphysis of fish, the pineal complex of anurans, and the parietal eye of reptiles contain well developed outer segments. Membrane stacks originate from a modified cilium and contain 50–150 disks, each with a thickness of approximately 28 nm. The length of the outer segments ranges from 2–4 μm in fish and amphibians (Fig. 3 a) and is much smaller than that of the retina with a diameter of approximately 50 μm . In these sensory pineal organs some degenerated outer segments are regularly found among many intact ones. The epiphysis cerebri of reptiles contains many degenerated outer segments and only a small number of

Fig. 3. a-e. Sensory structures in the pineal organ of *Rana catesbeiana*. a. Outer segment (OS) and inner segment (IS) of a pinealocyte projecting into the pineal lumen. * Modified cilium which is the origin for the lamellar disks of the cone-like outer segment. $\times 18,000$. b-e. Acetylcholinesterase-positive nerve cells in the pineal organ (P). b and c. The rostral part of the pineal organ consists of a ganglion-like accumulation of big nerve cells. d. Two different types of nerve cells, a big (*) and a small (▲) one are observed. e. * An accumulation of small nerve cells in the caudal region of the pineal organ. Some nerve cells (▲) are scattered around the tractus pinealis (TP) and the subcommissural organ (SCO). b. $\times 50$, c. $\times 300$, d. $\times 500$, e. $\times 150$

Fig. 4. a-c. *Milvus migrans leueatus* (Aves). **a.** No outer segments but well developed inner segments (IS) with many mitochondria and lysosome-like bodies of some pinealocytes (PC) project into the pineal lumen. The pinealocytes are separated by supporting cells (SC). $\times 8,400$. **b and c.** The inner segments were only modified cilia but no regular outer segments. $\times 30,000$

Fig. 5. Legend in opposite page.

differentiated ones. The pineal organ of birds contains only bulbous cilia (Fig. 4 b, c) or outer segments with irregular membrane structures (OKSCHE and VAUPEL-VON HARNACK, 1966). The mammalian pinealocyte shows no membrane structures; only some cilia are found (Fig. 5 d).

The inner segment of the pinealocytes in lower vertebrates shows an aggregation of mitochondria (Fig. 3 a, 4 a), microtubules and free ribosomes and is connected with the basal portion by a neck area (Fig. 2 a). The basal part of the cell is located within the parenchyma and contains a round nucleus, a well-developed Golgi complex and ergastoplasmic lamellae.

The basal process of the pinealocyte in lower vertebrates contains bundles of filaments, ribosomes, some mitochondria and vesicles with a diameter of 40 nm in the terminals, sometimes a small number of 100 nm granules. The basal processes of the pinealocytes terminate in a plexiform area, where they intermingle with dendrites of nerve cells and make synaptic ribbon contacts. The pattern of the nerve cells in the pineal organ of fish (WAKE, 1973; KORF, 1974), amphibians (WAKE et al., 1974) and birds (UECK and KOBAYASHI, 1972) is shown by the acetylcholinesterase method (Fig. 3 b-e). The axons of the nerve cells compose the tractus pinealis which connects the pineal organ with the brain. OKSCHE and associates (PAUL et al., 1971) traced the fibers to the periventricular gray and to the pretectal region. The photosensitivity of the pineal organ in fish, amphibians and of the parietal eye of reptiles has been indicated by electrical recordings; and inhibitory responses to light have been shown in the pineal ganglion cells as well as from the pineal tract in several species (see DODT, 1973). In the photoreceptive pinealocyte, hyperpolarized slow potentials induced by light were picked up by a microelectrode in the rainbow trout (TABATA et al., 1975). Besides the sensory function, however, there is also a secretory function in the pinealocytes of lower vertebrates. HAFEEZ and QUAY (1969) and OWMAN and RUEDEBERG (1970) in fish, OWMAN and associates (1970) in amphibians analyzed, with the fluorescence method of Falck-Hillarp and with microspectrofluorometric measurements, serotonin (a precursor of melatonin) in the pineal organ. AXELROD and his co-workers (1965) showed the enzymes synthesizing melatonin in the pineal of amphibians and VAN DE VEERDONK (1967) demonstrated melatonin in the pineal organ of amphibians with a bioassay test. The hormone synthesis is localized in the photosensitive photoreceptor, therefore this cell type has both sensory and secretory functions. In the phylogenetic evolution the mammalian pinealocyte has evolved from the sensory-secretory pinealocyte of lower vertebrates by reduction of the sensory

Fig. 5. a-f. Secretory and sensory structures of the mammalian pineal organ (Djungarian hamster, *Phodopus sungorus*). **a.** Light and dark pinealocytes are seen. Both cells show microtubules, the light pinealocyte many free ribosomes in the cytoplasm, the dark pinealocyte an accumulation of mitochondria. Between the two cells a cross section of a process of a pinealocyte or an autonomic nerve fiber. $\times 5,600$. **b.** Synthesis of 100 nm granules ($\uparrow$) in the Golgi apparatus (G) of a light pinealocyte. $\times 18,000$. **c.** Basal processes of pinealocytes with vesicles and dense-cored granules near the basal membrane and perivascular space. ($\blacktriangle$) Accumulation of vesicles ($\uparrow$) around a rosette-like structure. $\times 19,000$. **d.** A cilium projecting from one pinealocyte into the cell body of another pinealocyte. $\times 13,000$. **e.** Basal processes of pinealocytes in synaptic ribbon contacts ($\uparrow$) with processes of other pinealocytes. $\times 32,000$. **f.** Rosette-like structures and synaptic ribbon contacts ("neuro" hormonal synapses $\uparrow$) of a pinealocyte on the basal lamina near the perivascular space (PS). * Invaginated processes of pinealocytes containing vesicles and granules in direct contact with the basal membrane. $\times 14,000$.

structures and function.

3. Pinealocyte of mammals

Many studies have been done concerning the structure, innervation, biochemistry and function of the mammalian pineal organ and it is impossible to give an exhaustive list of references (see WURTMAN et al., 1968; KAPPERS, 1969, 1971; KAPPERS et al., 1974; WOLSTENHOLME and KNIGHT, 1971; QUAY, 1974).

In some mammalian species, for example in the rabbit, a cortex and a medulla are present in the pineal organ. This distinction is based on the distribution pattern of two different types of pineal cells, light and dark pinealocytes: both cell types are present in the medulla, whereas in the cortex only light pinealocytes occur (ROMIJN, 1973).

Light pinealocyte: The light pinealocyte is characterized by a frequently lobulated nucleus, many mitochondria of the crista type, numerous microtubules, closely spaced rough endoplasmic reticulum with regular shape, tubular smooth endoplasmic reticulum, clusters of free ribosomes and a well-developed Golgi complex. Three types of vesicles seem to be pinched off from the Golgi saccules: smooth-surfaced 35–120 nm gray vesicles; rough-surfaced gray vesicles (35–120 nm); and dense-cored vesicles (100–200 nm). Finally, electron-dense and electron-lucent droplets, probably lipids, and lysosome-like bodies can be found.

The light pinealocytes have several processes which terminate (1) in close relation with the cell body or the processes of dark pinealocytes, which are almost exclusively located around blood vessels (Fig. 2 c). Frequently the terminals are invaginated into the perikaryon of the dark pinealocytes, (2) between other light pinealocytes, (3) on the outer basal lamina of perivascular spaces.

Processes of light pinealocytes can leave the parenchyma to terminate freely within the perivascular space. The cytoplasm of cell body (Fig. 5 a) and of the processes contains dense-cored vesicles, mitochondria and bundles of microtubules running parallel with the axis of the process. The terminals are club-shaped and crowded with branched tubular smooth endoplasmic reticulum and electron-lucent vesicles measuring about 35–65 nm which are pinched off from the endoplasmic tubules. The dense-cored vesicles originate exclusively from the Golgi complex in the perikaryon (Fig. 5 b) and migrate in a distal direction into the terminals (Fig. 5 c).

There are two special structures present in the light pinealocytes: (1) rosette structures (LEONHARDT, 1967) and (2) vesicle-crowned (synaptic) ribbons. The rosette structure consists of an electron dense round "granule," lacking a limiting membrane and measuring 100–150 nm in diameter, surrounded by 8–12 grayish vesicles, showing a diameter of 40–60 nm. The central "granule" of the rosette structure originates from the Golgi complex, fuses with the plasma membrane and the gray vesicles disappear. According to LEONHARDT (1967), the gray vesicles contain secretory products, which are extruded either into the intercellular or into the perivascular space.

Synaptic ribbons (vesicles-crowned rodlets), generally present in the photoreceptive pinealocytes of lower vertebrates and in the rods and cones of the lateral eyes, can be regularly observed in the processes and their terminals of light pinealocytes (Fig. 5 e). They are closely surrounded by grayish vesicles (40–60 nm) varying in number. Rather often, small groups of these complexes lie either parallel or per-

pendicular to the cell membrane or they may lie deeper in the cytoplasm. The cell type lying adjacent to the area of a pinealocyte containing a vesicle-crowned ribbon, can either be a light or a dark pinealocyte. In the Djungarian hamster, *Phodopus sungorus*, synaptic ribbon contacts are often seen in direct contact to the basal lamina (Fig. 5f). VOLLRATH (1973) has shown circadian changes of the synaptic ribbons in the pineal organ of the guinea-pig.

Dark pinealocyte: Dark pinealocytes are exclusively observed in the pineal medulla of the rabbit (ROMIJN, 1973). They mainly surround the blood vessels and border the perivascular spaces. They send numerous long processes into the parenchyme where the processes intermingle with the light pinealocytes. The light pinealocytic terminals invaginate into the perikarya of the dark pinealocytes. The dark pinealocyte has a regularly oval shaped nucleus, the general pattern of mitochondria, a well-developed Golgi complex and gray vesicles. In contrast to the light pinealocytes, dense-cored vesicles are absent. The cisternae of the rough endoplasmic reticulum are enlarged and irregularly studded with ribosomes. Many free ribosomes are scattered throughout the cytoplasm. The presence of dense and lucent lipid-like droplets is obvious. The cytoplasm appears to be "dark," because of the presence of abundant very opaque particles, measuring 25–30 nm in diameter. These particles are larger and more dense than ribosomes and they do not represent glycogen. WARTENBERG and GUSEK (1965) named them "pigment granules." Besides the small particles, large membrane-bound pigment globules with a diameter of about 150–300 nm are present and also dark pigment bodies showing a diameter of 300–1,000 nm. The processes and their terminals contain pigment granules, mitochondria, microtubules and rough endoplasmatic reticulum.

ROMIJN (1973) presented the hypothesis that the light pinealocyte synthesizes a precursor compound which is released into the intercellular space, taken up by the dark pinealocyte and converted into a pineal-specific end-product; the hormonal end-product is released from the dark pinealocytes into the perivascular space, reaching the blood circulation. In the cortex of the pineal organ, which lacks dark pinealocytes, the precursor substance might directly enter the blood. This hypothesis must be proved.

4. Biochemistry of the pinealocyte

Indoles: LERNER and his co-workers (1958) isolated melatonin, 5 methoxy-N-acetyltryptamine, an active substance from bovine pineal extracts that caused the skin of amphibians to blanch (McCORD and ALLEN, 1917). The biosynthesis of melatonin in the pineal organ is well known (WURTMAN et al., 1968.) The substances and enzymes present in the pinealocytes are as follows:

transferase (HIOMT) 5-methoxy-N-acetyltryptamine (melatonin).

Melatonin is metabolized by the liver to 6-hydroxymelatonin and the hydroxylated melatonin is excreted as a glucuronide or sulphate conjugate. Serotonin is metabolized via two pathways: acetylation or deamination. Part of the deaminated indole is then oxidized to 5-hydroxyindole acetic acid and part is reduced to 5-hydroxytryptophol and further metabolized to 5-methoxytryptophol; the latter compound has effects on the rat gonad similar to those of melatonin (AXELROD, 1970).

Fig. 6. **a** and **b.** Autonomic nerve fibers in the pineal organ of *Phodopus sungorus*. **a.** An accumulation of dense-cored granules in sympathetic fibers located in the perivascular space $\times 12,000$. **b.** Bundle of unmyelinated nerve fibers with a myelinated fiber in the perivascular space; the myelinated fiber may be a preganglionic parasympathetic fiber. $\times 13,000$

Peptide/Polypeptide hormones: In the last few years biochemical results have indicated that the pineal organ forms and secretes polypeptide hormones. The pineal polypeptides are structurally very similar to vasopressin and oxytocin (PAVEL and PETRESCU, 1966; MOSZKOWSKA et al., 1971; BENSON and ORTS, 1972). Besides these small polypeptides, a polypeptide with a molecular weight of 100,000 was isolated (CHEESMAN and FORSHAM, 1974; OTA et al., 1975). Possibly the pineal polypeptides are transported within and released from the pinealocytes in conjunction with the carrier protein epiphysin (KRASS et al., 1971). The polypeptides seem to have much greater antigonadotropic activity than the indoles (REITER, 1976).

5. Neural control of the biochemical activity of the pinealocytes

A survey of the innervation of the pineal complex was given by KAPPERS (1965). More recently ROMIJN (1975) has shown two types of postganglionic nerve endings in the pineal organ of the rabbit: noradrenergic (sympathetic) and cholinergic (parasympathetic) fibers. The sympathetic innervation is well developed in the pineal organ of most species of birds (UECK, 1970, 1973) and mammals (OWMAN, 1965), but in the pineal organ of fish (OWMAN and RUEDEBERG, 1970) and amphibians (OWMAN et al., 1970) the number of sympathetic fibers is low (Fig. 1 b). Aminergic fibers from the central nervous system also reach the pineal organ of lower vertebrates (ALTNER, 1967; UECK, 1968, 1974) and make conventional synapses on the perikaryon of the pineal nerve cells (VIGH-TEICHMANN et al., 1973; Fig. 2b). In birds and mammals, the nerves branch in the pineal organ and the fibers either penetrate the basal lamina and come into an intimate contact with the pinealocytes, or the fibers are located only in the perivascular space (Fig. 6 a) and the transmitter (noradrenaline) diffuses through the basal lamina. Light mediates the transmitter release from the sympathetic fibers and the transmitter acts on the enzyme activity of the pineal organ. Thus the pineal organ is called a "neuro"-chemical or "neuro" endocrine transducer because it transforms a light input into a hormone output.

FISKE and her co-workers (1960) first showed that the weight of the pineal gland decreased when rats were exposed to continuous illumination. The pinealocytes were small in size and the cytoplasm contained only a few cytoplasmic basophilia; therefore, the environmental lighting influenced the pineal weight by depressing the synthesis of RNA and protein in the pinealocytes. This observation points to the influence of environmental lighting on the synthesis of a hormonal substance in the pineal organ. Light markedly reduces enzyme activity, especially of the NAT and

Fig. 7. Theoretical relationship between pineal indoles and pineal polypeptides. The synthesis of the indoles like melatonin originate from the amino acid tryptophane, the synthesis of the pineal polypeptides from different amino acids. Melatonin may inhibit either the formation (2) or release (3) of the polypeptide hormone(s) (4) and may have also the character of a hormone (1) (after REITER, 1976).

HIOMT, in the pineal organ.

How do messages of environmental lighting reach the pineal gland? In fish, amphibians and reptiles, the photoreceptive pinealocyte can respond to light; the pineals of birds have also sensory cells and a membranous lamellar complex suggestive of photoreceptor function (UECK et al., 1977). Mammalian pinealocytes have no photoreceptor structures. The light influences the hormone synthesis in the pinealocytes in an indirect way via the sympathetic nerve fibers. Using nerve transections and biochemical measurements of HIOMT activity (which is in darkness higher than in light), the nervous pathway through which light affects the pineal organ was established as follows: retina—inferior accessory optic tract—medial forebrain bundle—medial terminal nucleus of the accessory optic system—preganglionic sympathetic tract in the spinal cord—superior cervical ganglia—postganglionic fibers (nervi conarii)—pinealocyte. Lighting, via nerve impulses, modulates the liberation of noradrenaline from the sympathetic fibers. The amount of noradrenaline discharged to the parenchymal pineal cell then influences the synthesis of the hormone (melatonin). Noradrenaline might act indirectly by increasing the formation of cyclic AMP (AXELROD, 1970).

The serotonin and the noradrenaline contents of the pineal organ undergo striking diurnal changes. The level of serotonin is highest during the day (at 13:00) and is lowest at night (23:00). In continuous darkness, the rhythm persisted: the serotonin rhythm is thus endogenous (circadian) and driven by an internal (n. suprachiasmaticus?) biological clock. The noradrenaline content of the sympathetic fibers in the pineal organ is highest at night and lowest during the day. In continuous darkness, the noradrenaline rhythm in the pineal organ is abolished. Thus, in contrast to that of serotonin, the noradrenaline rhythm is exogenous and triggered by changes in environmental lighting rather than by an internal clock.

The cholinergic fibers may come from the superior salivatory nucleus and they are characterized by the presence of small clear 40 nm vesicles. The cholinergic axons penetrate the external basal lamina and end between the pinealocytes. Preganglionic parasympathetic fibers (Fig. 6 b) end on dendrites of parasympathetic neurons inside the pineal parenchyma (ROMIJN, 1975). The functional relationship of the parasympathetic fibers to the pinealocytes is still unknown.

6. The role of the pineal organ on the economy of the body

Knowledge about the influence of light on the pineal function gave rise to many experimental studies concerning the role of the pineal organ on the economy of the body (WURTMAN et al., 1968; KAPPERS, 1971, 1974; UECK, 1974). Rats remain in persistent vaginal estrus when kept in constant light; administration of extracts of bovine pineal glands reduces the occurrence of persistent estrus that is produced in continuous light. The pineal organ synthesizes an antigonadotropic substance; the synthesis of this compound is high in darkness and diminished under conditions of constant illumination. The facts that light has an influence on the NAT and HIOMT activity and that melatonin reduces the incidence of estrus in the rat, suggest that melatonin is an antigonadotropic substance. Continuous light causes persistent estrus by inhibiting the formation of a gonad inhibitor. Many other functional systems are discussed in relation to the pineal organ (REITER, 1973), but the effects seen by experiments are only slight. Therefore the pineal organ is called a "regulator of

regulators.”

In birds, the pineal function is also discussed in relation to the reproductive system and to the circadian locomotory rhythm (MENAKER and ZIMMERMAN, 1976); in fish in relation to body coloration, phototaxis, locomotory activity and reproductive system; and in amphibians to color change (see UECK, 1974).

When given to intact rats, melatonin usually inhibits sexual physiology and reverses the stimulatory effects of pinealectomy on the growth of the sexual organs (WURTMAN et al., 1968). But when melatonin was injected peripherally, effects were modest or completely lacking. When administered centrally melatonin depressed both pituitary and plasma levels of luteinizing hormone (LH). FRASCHINI and MARTINI (1970) found that melatonin and 5-hydroxytryptophol specifically inhibit LH release, while 5-methoxytryptophol and serotonin stimulate the release of follicle stimulating hormone (FSH). These authors located the receptors for the indoles in the hypothalamus and midbrain.

In the hamster, darkness is incapable of forcing regression of the neuroendocrine-reproductive axis if the animals have been pinealectomized (REITER, 1974). Melatonin, however, has no demonstrable inhibiting influences on either the growth or the function of the sexual organs. Melatonin may have an opposite effect, when given to hamsters as a subcutaneously implanted pellet; melatonin blocked the pineal gland from inducing atrophy of the testis and accessory organs. HOFFMANN (1974) found that in the Djungarian hamster, *Phodopus sungorus*, melatonin administration was capable of acting similar to a pinealectomy. Hoffmann's findings certainly are not consistent with observations that melatonin is the antigonadotropic factor found in the pineal organ. It seems that melatonin acts as an antigonadotropic factor in rats and as a progonadotropic factor in hamsters, but this explanation does not seem to suffice (REITER, 1976). A complete explanation would require pineal hormones other than melatonin. Other pineal antigonadotropic factors, mostly polypeptides, have been isolated (BENSON and ORTS, 1972; MOSZKOWSKA et al., 1971; OTA et al., 1975). Melatonin may act within the pineal gland itself to prevent either the formation or the discharge of the real antigonadotropic factor (REITER, 1976; Fig. 7). Further studies have yet to prove this hypothesis.

7. The pinealocyte—A liquor contacting neuron

VIGH and VIGH-TEICHMANN (1974) compared the structure of the pinealocyte in lower vertebrates and in mammals to the structure of cerebrospinal fluid (CSF) contacting neurons of the hypothalamus. The intraventricular dendritic endings of the CSF contacting neuron is similar to the inner segment of the pinealocyte, and the receptor-like atypical cilium of the CSF contacting neuron is comparable with the outer segment of the pinealocyte. Perikarya and axon-like processes of both cell types show the same main structures. Whether the CSF contacting neurons consist of mediator synapses similar to the synapses of the pinealocytes is still uncertain. The structural similarities of both cell types indicate that pinealocytes and CSF contacting neurons are related cell types. These relations include the pinealocytes of mammals, although they have no intimate contact with the ventricle as do the pinealocytes of most lower vertebrates; but the pinealocytes of mammals have contact with so-called reduced lumina (VIGH and VIGH-TEICHMANN, 1974) or canaliculi (KRSTIC, 1975).

8. The pinealocyte—A neurosecretory cell?

The difference between the ordinary neuron and the neurosecretory cell is pointed out by BARGMANN and SCHARRER: (1) the neurosecretory cell is a hormone-releasing cell and the hormone is transported in blood vessels or in the liquor cerebrospinalis; (2) transmitter substances of ordinary nerve cells, like acetylcholine or noradrenaline, act only in a narrow region adjacent to the effector cell and the effector time is short; and (3) the axons of the ordinary nerve cells contain enzymes in their terminals which are necessary to re-synthesize the transmitter after uptake of the components from the extracellular space. The terminals of the neurosecretory cells contain no hormone re-synthesizing enzymes and an uptake of the hormone does not exist.

Neurosecretory systems are: (1) the classical hypothalamo-hypophyseal system; (2) the releasing factor synthesizing neurons; (3) the liquor contacting neurons; (4) some of the circumventricular organs; (5) may be the aminergic system which sends its fibers from the hypothalamus to the eminentia mediana. In this case, it is not sure whether the fibers release the amine into the blood stream (if release occurs, then it could be a neurosecretion) or the fibers contact and influence only the peptidergic releasing factor containing fibers.

The pinealocytes synthesize the hormone in their perikaryon and transport it into the basal processes: The release of the hormone is into the blood stream. The basal processes do not contain the enzymes needed for the re-synthesis of the hormone. Therefore the pinealocytes are neuroendocrine cells, but probably no neurosecretory cells (BARGMANN, personal communication), because they might be no "real" nerve cells. But this must be proved more thoroughly. The pinealocytes of lower vertebrates possess, besides the hormone release, the ability to transmit impulses to dendrites of nerve cells as ordinary nerve cells do; they are compared with cones of the retina which are also called neurons (see BLOOM-FAWCETT, 1970). The pinealocytes of mammals have their phylogenetic origin from these photoreceptive pinealocytes and they still contain synaptic ribbon synapses (Fig. 5e); their similarities with liquor contacting neurons points to a narrow connection of the pinealocytes with neurosecretory cells. It is quite well known that the pineal organ has its ontogenetic origin from a thickening of the ependyma, but nothing is known till now of the origin of the pineal ganglion cells in lower vertebrates (Fig. 3b-e).

9. Pinealocyte—A paraneuron

It is shown in this small survey that the pinealocyte has its origin from the neuroectoderm, but it is not a real neuron (KAPPERS, 1971). Granules are synthesized in the Golgi complex and transported into the basal processes of the pinealocytes. A transmitter substance is released by synaptic ribbons, a peptide/polypeptide hormone is discussed in addition to the indol-derivates including melatonin. A direct or indirect light perception mediates the hormone synthesis and/or release. Therefore, the pinealocyte shows all the characteristics of paraneurons defined by FUJITA (1976).

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松果体細胞はパラニューロンか

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松果体は間脳の第三脳室上壁が管状に膨出して発生した器官で、その主たる構成細胞である松果体細胞 (pinealocyte) はニューロンではないが、神経性上皮に由来する。

松果体細胞は、下等脊椎動物では、網膜の視細胞と同様な外節を持ち、光を直接受容する。外節構造は系統発生の過程において次第に退化し、哺乳類ではもはや存在しない。光受容性の松果体細胞は僅かに内分泌機能を保有するが、は虫類から鳥類、哺乳類へと移行するに従い、内分泌機能は増強し、ゴルジ装置由来の分泌果粒が毛細血管に相対する細胞突起の終末に蓄積している。光受容性の松果体細胞は松果体に分布する知覚性ニューロンとの間にリボンシナプスを形成する。知覚性ニューロンは哺乳類松果体にはもはや存在しない。一方自律神経線維は光受容性松果体にはわずかに認められるに過ぎないが、鳥類、哺乳類には密に分布している。環境の光の影響下にある交感神経支配によって松果体細胞のホルモン合成に関与する酵素の活性が調節される。メラトニンのようなインドール誘導体の合成が証明され、ペプチドホルモンの存在が議論されている。

以上のように、松果体は神経-化学、神経-内分泌変換器、あるいは光入力（下等脊椎動物においては直接的に、哺乳類においては交感神経を介して）をホルモン出力に変換する光-神経-内分泌器官として機能する。松果体は光環境の歯車と噛み合った“生物時計”の役割を演じ、生体のいくつかの機能の調節器（または調節器の調節器）でもある。哺乳類では生殖機能との相関がよく知られている。松果体細胞は脳脊髄液接触ニューロンと神経分泌細胞とのそれぞれの特徴を兼ね備えている。また藤田恒夫（1976）の定義に従えばパラニューロンの一つであるとも云える。

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