

## THE PINEAL GLAND – A SYNOPSIS OF PRESENT KNOWLEDGE WITH PARTICULAR EMPHASIS ON ITS POSSIBLE ROLE IN CONTROL OF GONADOTROPHIN FUNCTION

B.K. Knight, M.M.M. Hayes and R.B. Symington

*Department of Anatomy, University of Rhodesia*

A fundamental principle of anatomy is that structure and function are related intimately. Thus, to understand the function of an organ, a knowledge is required of its structure both at macro- and micro- anatomical levels. Until comparatively recently, surprisingly little was known about pineal structure, even in laboratory animals, and as a consequence, very little was known with certainty about its function. However, in the light of recent advances in this field, the pineal is now known to be, in general terms, a “neuro-endocrine transducer”, i.e. the pineal receives neural stimuli and transforms them into a hormonal output (Wurtman & Anton-Tay, 1969). Further, of the many functions attributed to the pineal, the most widely investigated activity of the gland is its involvement in partial control of gonadotrophin secretion (Anton-Tay, 1971; Moszkowska, Kordon & Ebels, 1971). However, work on the pineal is still in its comparative infancy and many important questions about its anatomy and hence its function remain unsolved. Thus, for example, four important questions are:

- i. How are the hormonal products transported from the gland, what is their chemical composition and what are their target organs?
- ii. How is the pineal innervated and what effect does this innervation have on pineal function?
- iii. What effect(s), if any, do environmental factors such as temperature or photoperiod have on pineal function?
- iv. What is the effect of increasing age on pineal structure? Do such changes have any relation to sexual maturation, growth propensity and therefore, to animal production?

Patently, thorough investigation and knowledge of pineal structure is essential to an understanding of and further elucidation of pineal function. The purpose of this paper is to review the state of present knowledge of pineal structure in the bovine and relate this where possible to function.

### Review of Literature

#### Phylogenic evolution of the pineal

During its phylogenic development, pineal morphology and function have changed extensively. In lower vertebrates, the pineal is a photoreceptive organ very similar to the eye, with its functional cells closely resembling the rods and cones of the retina. In such species, the function of the “gland” is mediated by a nervous pathway – “the pineal tract” – (Kappers 1971). In other words, in lower vertebrates the pineal is a sense organ.

In reptiles and birds, the photoreceptive nature of the pineal is much reduced and cells have become partially

secretory. Thus, in these phyla, secretory activity is controlled by the direct reception of photic stimuli by the cells themselves. In some birds, however, the pineal cells are also controlled indirectly by neural stimuli reaching the gland via the autonomic nervous system (Kappers, 1971).

In mammals, photoreceptive function has apparently been lost completely and the functional cells (pinealocytes) are entirely secretory in nature. Here, pinealocyte function is controlled by indirect photic stimuli. As a consequence of this innervation, the pineal could very well be an organ capable of cyclic endocrine activity under the control of the photoperiod. Thus the pineal could be considered as a “biological clock” controlling circadian and other rhythms.

#### Gross anatomy

In bovines, the pineal measures about 15 mm. by 5 mm. The gland is an evagination of the diencephalic roof of the third ventricle and lies in close relation to the habenular and posterior commissures (Fig. 1). The pineal recess (PR) of the third ventricle lies in the lower extremity of the gland between the habenular and posterior commissures (Fig. 1) and reaches into the lowermost part of the parenchyma of the gland. On the dorsal aspect of the gland, prolongations of the third ventricle forms a supra-pineal recess (SPR). The close relationship of much of the surface of the pineal to cerebrospinal fluid (CSF) of the third ventricle has led to the suggestion that pineal hormones may be secreted into the CSF en route to the hypothalamus, (*inter alia*, Sheridan, Reiter & Jacobs, 1969; Symington, Knight & Hayes, 1972).

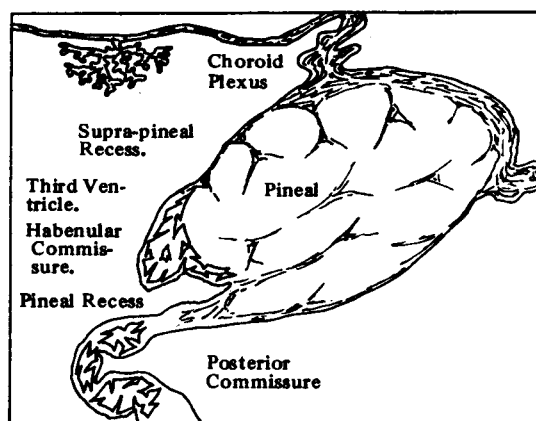


Fig. 1 – *The Gross Anatomy of the Bovine Pineal.*

Micro-anatomy (*inter alia* Anderson, 1965).

The bovine pineal is a richly vascularised gland, encapsulated by thick pia. Trabeculae from the capsule invade the gland and divide the parenchymia into irregular, indistinct lobules. Blood enters the gland in and is distributed by vessels which run in the connective tissue trabeculae. Two main types of cell occur in the parenchyma: pinealocytes and glial cells.

#### Pinealocytes – Light Microscopy

Pinealocytes are large cells with numerous basophilic cytoplasmic processes. The processes are tortuous and end in contact with other pinealocytes, glial cells, freely or on the basement membrane of peri-vascular spaces. Pinealocytes possess large folded nuclei, each with a massive, basophilic nucleolus.

#### Pinealocytes – Electron Microscopy

The most striking aspect of pinealocyte ultrastructure in the bovine is the presence of abundant microtubules of diameter 22 to 23 nm. These tubules form a randomly disposed mesh in the body of the pinealocyte, but come to lie in a parallel orientation down the cell processes. The microtubules are sometimes continuous with small vesicles. Large amounts of smooth-surfaced endoplasmic reticulum and free ribosomes are seen in the cell cytoplasm. Mitochondria are numerous. Cells show a Golgi complex which is associated with electron-dense cored, clear-haloed vesicles. It is of particular interest that similar such cells occur in the adrenal medulla (Yates, 1963), and in the carotid body (Rogers, 1963). Electron microscopic studies of pinealocyte processes reveal the presence of numerous pinocytotic caveolae in the plasma membrane. The processes end in bulbous swellings and can be identified by the presence of many mitochondria, microtubules and vesicles.

#### Glial Cells – Light Microscopy

Glial cells are large, multiprocessed cells which are usually placed singly and randomly within the parenchyma of the gland. These cells have a prominent oval or round nucleus and cytoplasm is more basophilic than that of pinealocytes.

#### Glial Cells – Electron Microscopy

Glial cells possess a scant microtubular component, the tubules being 23 to 27 nm. in diameter. A characteristic and definitive abundance of microfibrils (5 to 6 nm. in diameter) occurs in these cells. The filaments are randomly placed in the cell body but lie in parallel orientation in the cell processes. Large amounts of rough-surfaced endoplasmic reticulum occur in the glial cytoplasm and free ribosomes are also seen. Dilated cisternae are associated with the endoplasmic reticulum. Glycogen granules are present in association with smooth-surfaced endoplasmic reticulum of the cell.

Mitochondria (identifiably different in shape from those in pinealocytes) and single membrane-limited bodies of various sizes occur in the glial cytoplasm. Glial cells also possess a Golgi complex. The glial processes, which contain glycogen, appear to contact, and/or encircle other glial and pinealocytic processes or blood vessels. At such points of contact, *maculae adhaerents* and *zona occludentes* ensure close contiguity between these cells. Glial processes end as bulbous expansions filled with glycogen.

#### Innervation

The origin of nerve fibres reaching the pineal in the bovine is conjectural. As a consequence, the effect that the innervation may have on the gland is also conjectural. However, it is widely accepted that the mammalian pineal is innervated by autonomic fibres arising in the superior cervical ganglion. In other words, the pineal is an end organ of the peripheral nervous system, situated in the central nervous system – a truly unique condition (Kappers, 1971). The autonomic fibres reach and are distributed in the gland via its vasculature.

Photic control over the pineal is mediated by these sympathetic fibres. In species investigated to date, fibres of the optic nerve form the interior accessory optic tract before the optic chiasma (Truex & Carpenter, 1970). The nerves run through the mid-brain, synapse in the medial terminal nucleus and run through the hind brain to the intermediate thoracic nucleus of the spinal cord. In turn, fibres from this nucleus run to the superior cervical ganglion and thence to the pineal.

Anderson (1965) has reported the presence of a tract of nerve fibres which enters the bovine pineal from the habenular commissure. The ultimate origin of these fibres is unknown and so the type of control that these fibres could mediate is also unknown.

#### Blood supply

The immediate source of blood reaching the pineal is unknown. It seems reasonable to assume that the pineal is supplied by vessels which arise from the posterior choroideal artery. This vessel takes origin from the posterior cerebral artery and runs past the pineal gland to the choroid plexus of the third ventricle. Venous drainage occurs via the adjacent great cerebral vein and straight sinus. Capillaries of the gland are not fenestrated in the bovine (Anderson, 1965), although pinealocytes and glial cells end in close relationship with the basement membrane of the vessels.

#### Discussion

The rich blood supply of the pineal suggests that the gland is highly active metabolically, an observation substantiated by the structure of the pinealocytes themselves (as seen using both electron and light microscopy). Thus, the massive nucleolus and the numerous mitochondria, ribosomes, a Golgi complex, endoplasmic reticulum and vesicles indicate an intense synthetic activity in pinealocytes. The electron-dense cored, clear-haloed vesicles of the pinealocyte

appear to be similar to those vesicles found in the carotid body (Rogers, 1963) and the adrenal medulla (Yates, 1963). In the latter instance, the vesicles are thought to contain catecholamines (Lentz, 1971). Since the bovine pineal contains considerable amounts of indoleamines (McIsaac, Farrell, Taborsky & Taylor, 1965) and since indoleamines are chemically similar to catecholamines, it is possible that the electron-dense cored, clear-haloed vesicles in the pineal contain indoleamines. That all these structures (i.e. adrenal medulla, carotid body and pineal) are derived from neuroectoderm and all have argentophilic cells, lends credence to this concept.

Using the same arguments as for pinealocytes, the ultrastructure of the glial cells in the pineal also supports the view that the pineal is a very active organ. Further, an interesting relationship is evident between pinealocytes and glial cells. The presence of glycogen in the glial cells suggests that these cells may play a role in the provision of nutrients for pinealocytes. Such a relationship has been shown to exist between neurons and glial cells in the central nervous system (Hydén & Pigon, 1960; Hydén & Lange, 1964). Of particular interest in this context is the close relationship between and the joining together of pinealocytes and glial processes by *zona occludentes*. Kanno & Loewenstein (1964) reported that inter-cellular junctions (e.g. *zona occludentes*) provide an area of high permeability in the cell membrane. Thus, Anderson (1965) suggested that the *zona occludentes* between the closely opposed pinealocytic and glial processes provide a means of rapid and easy interchange of ions and nutrients between these cells. Study of pineal microstructure in humans (Quay, 1965; Symington, et al. 1972) and in the rat (Quay, 1972) has indicated that a similar nutritive relationship between pineal glial cells and pinealocytes also exists in these species.

In the light of the embryonic origin of the pineal and of its phylogenetic evolution, it would not be surprising that pinealocytes bear many structural similarities to neurons. Both pinealocytes and neurons are argentophilic and are multiprocessed. The processes of both end in bulbous swellings which contain numerous mitochondria and vesicles. Both cell-types possess an extensive microtubular component which appears to enter the cell process from the cell body and run to the bulbous endings of the processes. In neurons, the microtubular component presumably transports neurotransmitters along the axons to the end feet for storage in presynaptic vesicles. A similar role has been proposed for the microtubules of neurosecretory neurons which secrete hormones from their endings. Anderson (1965) speculated upon the rôle of microtubules in pinealocytes as either transporting or supporting. In the light of the similarities between pinealocytes and neurons and since vesicles are associated closely with microtubules in the

pinealocyte, it seems possible that the microtubules of the pinealocyte may be involved with intra-cellular transport. The process of secretion of pineal hormones may thus be compared with secretion of neurotransmitters and neurohormones. Indeed, a progressive trend toward secretion of hormones by cells of neuroectodermal origin could be envisaged from neuron to neurosecretory neuron to pinealocyte.

The exposure of much of the pineal to cerebrospinal fluid (CSF) has led to the suggestion that pineal hormones may be secreted directly into the CSF to facilitate transport of the hormones to the hypothalamus, (*inter alia* Sheridan, et al 1969; Symington, et al. 1972). This suggestion is supported by both anatomical (Knigge, Scott & Weindl, 1972; Symington, et al. 1972) and physiological (Wurtman, 1971; Anton-Tay, 1971) evidence. The advantages of a CSF route for pineal hormones to reach the hypothalamus are obvious. Thus, since the pineal hormones would not be subject to rapid deactivation by the liver, (melatonin has a half life of 25 minutes in systemic blood), the direct CSF route would allow lower levels of hormone production by the relatively small pineal. Again, dilution of the pineal hormones would be less in the CSF than in the blood. This would allow a greater concentration of the hormone in the area of the hypothalamus than otherwise, and so enhance and perhaps accelerate the response of the hypothalamic receptors to the hormones. Finally, the CSF route would afford a means to prevent the pineal hormones having undesirable effects on peripheral organs.

The significance of the mode of innervation of the pineal is conjectural. However, in the light of the phylogenetic evolution of the pineal and of work on ferrets (Herbert, 1971) and rats (*inter alia*, Roth, Wurtman & Altschule, 1962), the possibility exists that the pineal is a "biological clock". The bovine pineal is known to produce anti-gonadotrophic principles which affect the hypothalamus and the anterior pituitary (Hayes, Knight & Warton, 1973). Thus, the photoperiod may well affect reproduction in animals via the pineal. Indeed, the effect of photoperiod on reproduction in sheep (Yeates, 1949) may well be modulated in this manner.

A corollary to this concept is the possibility that the level of endocrine activity in the pineal changes with age. In many species, degenerative changes such as calcification, increased connective tissue lobulation and the formation of cysts and large scars of glial cells in the pineal parenchyma have been reported (*inter alia*, Tapp & Huxley, 1972; Symington, et al. 1972). Thus, the antigonadotrophic activity of the pineal may decrease with age and hence a pineal mechanism controlling sexual maturation, growth propensity and therefore animal productivity is possible.

## References

- ANDERSON, E., 1965. The anatomy of ovine and bovine pineals. *J. Ultrastr. Res.* Suppl. 8.  
ANTON-TAY, F., 1971. Pineal Brain Interrelations. In *The Pineal Gland*, Ciba Symposium. London: Churchill.  
HAYES, M.M.M., KNIGHT, B.K., & WARTON, C.M.R., 1973. Preliminary studies on the functional relationship between pineal, hypothalamus and adenohypophysis using bovine tissue in organ culture. *C. Afr. J. Med.* 19 193.

- HERBERT, J., 1971. The role of the pineal gland in the control by light of the reproductive cycle of the ferret. In *The Pineal Gland*, Ciba Symposium, London: Churchill.
- HYDEN, H. & LANGE, P., 1964. Rhythmic enzyme changes in neurons and glia during sleep and wakefulness. *Life Sci.* 3, 1215.
- HYDEN, H. & PIGON, A., 1960. Cytophysical study of the functional relationship between oligodendroglia and neurons. *J. Neurochem.* 6, 57.
- KANNO, V. & LOEWENSTEIN, W.R., 1964: Low resistance coupling between gland cells. Some observations on inter-cellular contact membranes and inter-cellular spaces. *Nature, Lond.* 201: 194.
- KAPPERS, J.A., 1971. The Pineal Gland – an introduction. In *The Pineal Gland*, Ciba Symposium. London: Churchill.
- KNIGGE, K.M., SCOTT, D.E. & WEINDL, A., 1972: Editors, Brain-Endocrine Interaction, Median Eminence: Structure and Function. *International Symposium, S. Karger.*
- LENTZ, T.L., 1971. In *Cell Fine Structure*. Philadelphia: W.B. Saunders.
- McISAAC, W.M., FARRELL, G., TABORSKY, R.G. & TAYLOR, A.W., 1965. Indolecompounds: Isolation from pineal tissue. *Science*, 148, 102.
- MOSZKOWSKA, A., KORDON, C. & EBELS, I., 1971. Pineal control of gonadotrophin release. In *The Pineal Gland*, ciba Symposium. London: Churchill.
- QUAY, W.S., 1965. Histology and cytology of the mammalian pineal. *Recent Prog. Brain Res.* 10, 49.
- QUAY, W.B., 1972. Twenty four hour rhythmicity in carbonic anhydrase activity of choroid plexus and the pineal gland. *Anat. Rec.* 174, 279.
- ROGERS, D.C., 1963. Distinctive cell types in the amphibian carotid labyrinth. *Nature, Lond.* 200, 492.
- ROTH, W.D., WURTMAN, R.J. & ALTSCHULE, M.D. 1962. Morphological changes in the pineal with photoperiod changes. *Endocrinology*, 71, 888.
- SHERIDAN, M.N., REITER, R.J. & JACOBS, J.J., 1969. The anatomical relation of the hamster pineal to the third ventricle. *J. Endocr.* 45, 131.
- SYMINGTON, R.B., KNIGHT, B.K. & HAYES, M.M.M., 1972. Microstructure of the pineal gland in man and baboon (*Papio ursinus*). *Ann. Meet. Anat. Soc. Great Britain and Ireland.* Dec. 1972.
- TAPP, E. & HUXLEY, M., 1972. The histological appearance of the human pineal gland from puberty to old age. *J. Path.* 103, 137.
- TRUEX, R.C. & CARPENTER, M.B., 1969. In *Human Neuroanatomy*, Baltimore: Williams and Wilkins.
- WURTMAN, R.J., 1971. General discussion. In *The Pineal Gland*, Ciba Symposium. London: Churchill.
- WURTMAN, R.J. & ANTON-TAY, F., 1969. The mammalian pineal as a neuroendocrine transducer. *Rec. Prog. Hormone Res.* 25, 493.
- YATES, R.D., 1963. An electron microscopic study of the effects of reserpine on adreno-medullary cells of the Syrian hamster. *Anat. Rec.* 146, 29.
- YEATES, N.T.M., 1949. Breeding season of the sheep. *J. agric. Sci.* 39: 1