Pineal gland

The **pineal gland**, **conarium**, or **epiphysis cerebri**, is a small unpaired endocrine gland in the brain of most vertebrates. The pineal gland produces melatonin, a serotonin-derived hormone which modulates sleep patterns in both circadian and seasonal cycles. The shape of the gland resembles a pine-cone from which it derived its name (Douglas Herper, 2018). The pineal gland is located in the epithalamus, near the center of the brain, between the two hemispheres, lodged in a groove where the two halves of the thalamus join (Macchi MM, Bruce JN 2004; Arendt J, Skene DJ, 2005). The pineal gland is one of the neuro-endocrine secretory, circum-ventricular organs in which capillaries are mostly permeable to solutes in the blood (Gross PM & Weindl A, 1987)

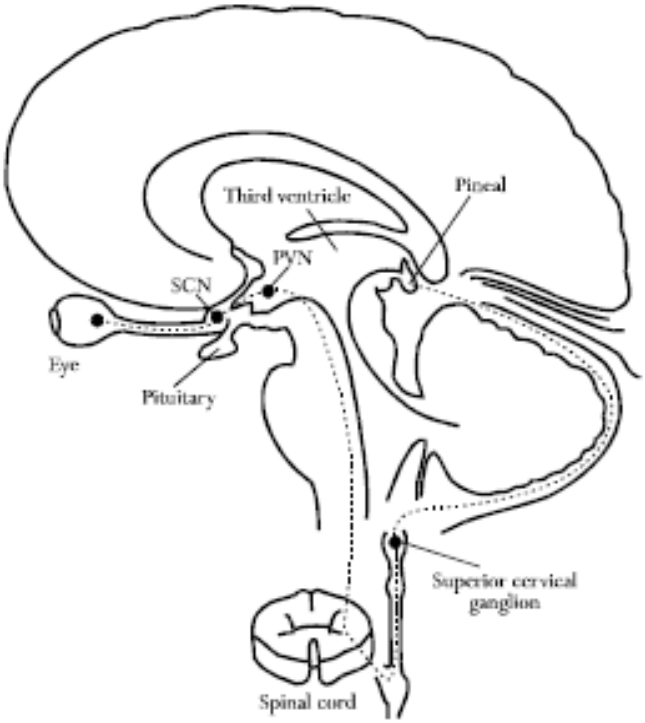

Figure 1.16 Schematic overview of the location of the pineal gland in the human brain, as well as its innervation and some important tissues involved in the various physiological effects of melatonin. (SCN = suprachiasmatic nucleus, PVN = paraventricular nucleus)

Anatomy and histology:

The gland is reddish-gray and about the size of a grain of rice (5–8 mm) in humans. The pineal gland, also called the pineal body, is part of the epithalamus, and lies between the laterally positioned thalamic bodies and

behind the habenular commissure. It is located in the quadrigeminal cistern near to the corpora quadrigemina (Chen C.Y. *et al,* 1998). It is also located behind the third ventricle and is bathed in cerebrospinal fluid supplied through a small pineal recess of the third ventricle which projects into the stalk of the gland.

Blood supply

Unlike most of the mammalian brain, the pineal gland is not isolated from the body by the blood–brain barrier system; Pritchard TC, Alloway KD, 1999). it has profuse blood flow, second only to the kidney,(Arendt J, 1995) supplied from the choroidal branches of the posterior cerebral artery.

Nerve supply

The pineal gland receives a sympathetic innervation from the superior cervical ganglion. A parasympathetic innervation from the pterygopalatine and otic ganglia is also present.[15] Further, some nerve fibers penetrate into the pineal gland via the pineal stalk (central innervation). Also, neurons in the trigeminal ganglion innervate the gland with nerve fibers containing the neuropeptide PACAP.

Histology: The pineal body consists in humans of a lobular parenchyma of pinealocytes surrounded by connective tissue spaces. The gland's surface is covered by a pial capsule. The pineal gland consists mainly of pinealocytes, but four other cell types have been identified. As it is quite cellular (in relation to the cortex and white matter), it may be mistaken for a neoplasm (Kleinschmidt-DeMasters BK & Prayson RA, 2006).

Pinealocytes: The pinealocytes consist of a cell body with 4–6 processes emerging. They produce and secrete melatonin. The pinealocytes can be stained by special silver impregnation methods. Their cytoplasm is lightly basophilic. With special stains, pinealocytes exhibit lengthy, branched cytoplasmic processes that extend to the connective septa and its blood vessels.

Interstitial cells: Interstitial cells are located between the pinealocytes. They have elongated nuclei and a cytoplasm that is stained darker than that of the pinealocytes.

Perivascular phagocytes: Many capillaries are present in the gland, and perivascular phagocytes are located close to these blood vessels. The perivascular phagocytes are antigen presenting cells.

Pineal neurons: In higher vertebrates neurons are usually located in the pineal gland. However, this is not the case in rodents.

Peptidergic neuron-like cells: In some species, neuronal-like peptidergic cells are present. These cells might have a paracrine regulatory function.

Development:

The human pineal gland grows in size until about 1–2 years of age, remaining stable thereafter,(Schmidt F,1995; Sumida M, *et al.,*1996) although its weight increases gradually from puberty onwards (Tapp E & Huxley M, 1971, 1972). The abundant melatonin levels in children are believed to inhibit sexual development, and pineal tumors have been linked with precocious puberty. When puberty arrives, melatonin production is reduced.

Pineal indoleamine biosynthesis:

The biosynthesis of pineal indolamine synthesis is well documented (Klein DC. *et al.*, 1997; Stehle JH., 1995; Stumpf WE., 1988). It takes in following steps (Figure…..):

1. The amino acid tryptophan is converted to 5-hydroxytryptophan by the the enzyme tryptophan hydroxylase.
2. 5-hydroxytryptophan is then acted upon by decarboxylase enzyme to form 5-hydroxytryptamine (5-HT, Serotonin).
3. The 5-HT, serotonin is then converted to N-acetylserotonin by the action of the enzyme N-acetyltransferase.
4. The N-acetylserotonin produced is then O-methylated by hydroxyindole-O-methyltransferase (HIOMT) to form N-acetyl-5-methoxytreptamine (Melatonin).

Figure…..

Metabolism of melatonin: Melatonin is metabolized in the liver to a glucuronide for urinary excretion.

Although acetylation to N-acetylserotonin is a necessary step in the synthesis of melatonin, deamination of serotonin by monoamine oxydase can also occur in the pineal. The deaminated product may be either oxidized to 5-hydroxyindoleacetic acid or reduced to 5-hydroxytryptophol. These compounds produced then can become O-methylated by HIOMT to give 5-methoxyindole acetic acid and 5-methoxytryptophol.

Regulation of Indolamine biosynthesis: Melatonin biosynthesis is mainly controlled by N-acetyltransferase activity. However, HIOMT activity is also considered to be of prime importance.

1.Effect of light on pineal indoleamine biosynthesis:

Light has profound effect on melatonin secretion. In the absence of light at night, there is an elevated level of melatonin secretion due to increased activity(10-100 times greater) of N-acetyltransferase, leading to subsequent increase in concentration (10-30 times) of N-acetylserotonin and activity of HIOMT.

Pineal serotonin level shows marked diurnal changes, with highest level noted during the daylight hours. The levels are depressed at night because serotonin is the substrate for N-acetyltransferase action and therefore converted to N-acetylserotonin. Reversal of external lighting conditions reverses the rhythm of pineal enzyme activity and biosynthesis of indolamine. Thus, a daily diurnal rhythm of pineal biosynthetic activity is observed and is controlled by the normal day-to-day changes in natural lighting.

2.CNS pathway in the control of pineal indolamine biosynthesis:

Melatonin is synthesized in response to norepinephrine released from postganglionic neurons from the superior cervical ganglia. Therefore, pineal gland is considered to be a **neuroendocrine transducer** because the neural input in this organ is converted into an endocrine output (Wurtman RJ *et al.,*1968). Postganglionic stimulation of pinealocytes depends on the absence of light activation of the retina of the lateral eyes.Information of light perceived by the eyes is conveyed to the '**Suprachiasmatic nuclei'** (SCN) of the brain via a retino-hypothalamic pathway (Moore RY, 1978).The pineal gland is the intermediary between the external photoperiod and internal mileu. It is the site at which information about light and dark is translated or transduced into a chmical messenger (Reiter RJ, 1991).

Neuronal circuits from SCN convey information via the medial forebrain bundle to the upper thoracic spinal cord and then out to the superior cervical ganglia. From these ganglia, the postganglionic neurons proceed to innervate the pineal. There are evidences that SCN is the CNS site responsible for generation of the nocturnal activity of pineal indolamine biosynthesis in mammals. The circadian oscillatory activity of the cells of the suprachiasmatic nuclei may be entrained to the daily photoperiod.

3.Intracellular control of pineal indolamine biosynthesis:

When supracervical postganglionic neurons release norepinephrine, it interacts with pinealocyte β-adrenoceptors, which leads to an increase in pineal cAMP production (Rosebloom PH and DC Klein, 1995). Elevation of this intracellular second messenger results in conversion of tryptophan to serotonin and then serotonin to N-acetylserotonin.

Physiological role of Pineal gland:

The primary function of the pineal gland is to produce melatonin. Melatonin has various functions in the central nervous system, the most important of which is to help modulate sleep patterns. Melatonin production is stimulated by darkness and inhibited by light (Lowrey PL, Takahashi JS, 2000). Light sensitive nerve cells in the retina detect light and send this signal to the suprachiasmatic nucleus (SCN), synchronizing the SCN to the day-night cycle. Nerve fibers then relay the daylight information from the SCN to the paraventricular nuclei (PVN), then to the spinal cord and via the

sympathetic system to superior cervical ganglia (SCG), and from there into the pineal gland.

Besides this, melatonin has multiple physiological roles in following life processes such as regulation of Circadian Rhythms, regulation of Breeding cycle, regulation of pigmentation, regulation of Immune System, modulation of neural Functions, has anti-oxidant properties, anti-cancer Properties, regulation of Aeging, regulation of behavior and regulation of endocrine glands.

The compound pinoline is also claimed to be produced in the pineal gland; it is one of the beta-carbolines (Callaway JC *et al.,* 1994). This claim is subject to some controversy.

Role of pineal gland in regulation of the pituitary gland:

Studies on rodents suggest that the pineal gland influences the pituitary gland's secretion of the sex hormones, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Pinealectomy performed on rodents produced no change in pituitary weight, but caused an increase in the concentration of FSH and LH within the gland Administration of melatonin did not return the concentrations of FSH to normal levels, suggesting that the pineal gland influences pituitary gland secretion of FSH and LH through an unknown transmitting molecule(*Motta M, et al.,*1967). .

The pineal gland contains receptors for the regulatory neuropeptide, endothelin -1,(Naidoo V. *et al.*, 2004) which, when injected in picomolar quantities into the lateral cerebral ventricle, causes a calcium-mediated increase in pineal glucose metabolism (Gross PM, *et al.,* 1993).

Role of pineal gland in regulation of bone metabolism.

Studies in mice suggest that the pineal-derived melatonin regulates new bone deposition. Pineal-derived melatonin mediates its action on the bone cells through MT2 receptors. This pathway could be a potential new target for osteoporosis treatment as the study shows the curative effect of oral melatonin treatment in a postmenopausal osteoporosis in mouse model (Sharan K, *et al.,* 2017)

Pathophysiology:

Calcification

Computer tomogralhical study revealed that calsification of the pineal gland is typical in young adults, and has been observed in children as young as two years of age (Zimmerman RA, 1982). The internal secretions of the pineal gland inhibit the development of the reproductive glands because when it is severely damaged in children, development of the sexual organs and the skeleton are accelerated (Gray's anatomy, 2012). Pineal gland calcification is detrimental to its ability to synthesize melatonin (Kunz D. *et al., 1999;* Tan, Dun Xian *et al.,* 2018) but has not been shown to cause sleep problems (*Del Brutto et al.,* 2014).

The calcified gland is often seen in skull x-rays. Calcification rates vary widely by country and correlate with an increase in age, with calcification occurring in an estimated 40% of Americans by age seventeen. Calcification of the pineal gland is associated with corpora arenacea, also known as "brain sand" (Zimmerman RA, 1982).

Tumors

Tumors of the pineal gland are called pinealomas. These tumors are rare and 50% to 70% are germinomas that arise from sequestered embryonic germ cells. Histologically they are similar to testicular seminomas and ovarian dysgerminomas (Kumar V *et al.,* 2014).

A pineal tumor can compress the superior colliculi and pretectal area of the dorsal midbrain, producing Parinaud's syndrome. Pineal tumors also can cause compression of the cerebral aqueduct, resulting in a non-communicating hydrocephalus. Other manifestations are the consequence of their pressure effects and consist of visual disturbances, headache, mental deterioration, and sometimes dementia-like behavior (Bruce J. 2015).

These neoplasms are divided into three categories, pineo-blastomas, pineo-cytomas, and mixed tumors, based on their level of differentiation, which, in turn, correlates with their neoplastic aggressiveness (American brain tumor association, 2015). The clinical course of patients with pineo-cytomas is prolonged, averaging up to several years (Clark AJ, 2010). The position of these tumors make them difficult to remove surgically.

Other conditions

The morphology of the pineal gland differs markedly in different pathological conditions. For instance, it is known that its volume is reduced both in obese patients as well as patients with primary insomnia (Tan Dun Xian, 2018).

Other animals

Most living vertebrates have pineal glands. It is likely that the common ancestor of all vertebrates had a pair of photosensory organs on the top of its head, similar to the arrangement in modern *lampreys* (Cole WC & Youson JH 1982). Some extinct Devonian fishes have two parietal foramina in their skulls, (Cope ED,1888; Schultze H, 1993), suggesting an ancestral bilaterality of parietal eyes. The parietal eye and the pineal gland of living tetrapods are probably the descendants of the left and right parts of this organ, respectively (Dodt E, 1973).

During embryonic development, the parietal eye and the pineal organ of modern lizards (Tosini G, 1997) and tuataras (Dendy A, 1911) form together from a pocket formed in the brain ectoderm. The loss of parietal eyes in many living tetrapods is supported by developmental formation of a paired structure that subsequently fuses into a single pineal gland in developing embryos of

turtles, snakes, birds, and mammals (Quay WB 1979; London academic press, 2017).

The pineal organs of mammals fall into one of three categories based on shape. Rodents have more structurally complex pineal glands than other mammals (Vollrath L,1979).

Crocodilians and some tropical lineages of mammals, some xenarthrans (sloths), pangolins, sirenians (manatees & dugongs), and some marsupials (sugar gliders) have lost both their parietal eye and their pineal organ(*Ralph CL 1975,* Vollrath L,1979, *Ralph C, 1985).*

Polar mammals, such as walruses and some seals, possess unusually large pineal glands.

All amphibians have a pineal organ, but some frogs and toads also have what is called a "frontal organ", which is essentially a parietal eye (Adler K, 1976).

Pinealocytes in many non-mammalian vertebrates have a strong resemblance to the photoreceptor cells of the eye. Evidence from morphology and developmental biology suggests that pineal cells possess a common evolutionary ancestor with retinal cells.

Pineal cytostructure seems to have evolutionary similarities to the retinal cells of the lateral eyes (Klein DC 2004). Modern birds and reptiles express the phototransducing pigment melanopsin in the pineal gland. Avian pineal glands are thought to act like the suprachiasmatic nucleus in mammals (Natesan A *et al.*, 2002). The structure of the pineal eye in modern lizards and tuatara is analogous to the cornea, lens, and retina of the lateral eyes of vertebrates (Quay W.B., 1979).

In most vertebrates, exposure to light sets off a chain reaction of enzymatic events within the pineal gland that regulates circadian rhythms (Moore RY, *et al.*, 1969) In humans and other mammals, the light signals necessary to set circadian rhythms are sent from the eye through the retinohypothalamic system to the suprachiasmatic nuclei (SCN) and the pineal gland.

The fossilized skulls of many extinct vertebrates have a pineal foramen (opening), which in some cases is larger than that of any living vertebrate (Edinger T, 1955). Although fossils seldom preserve deep-brain soft anatomy, the brain of the Russian fossil bird *Cerebavis cenomanica* from Melovatka, about 90 million years old, shows a relatively large parietal eye and pineal gland (Kurochkin E.N. *et al.,* 2007).