Raja N. L. Khan Womens' College (Autonomous)

Zoology (H), 6th SEM, Paper DSE3T-Endocrinology

by M. Malik Mukherjee

Pineal Gland

Study areas:

A. Structure of Pineal Gland,

B. Secretion of Pineal Gland,

C. Functions- In Biological Rhythms & Reproduction.

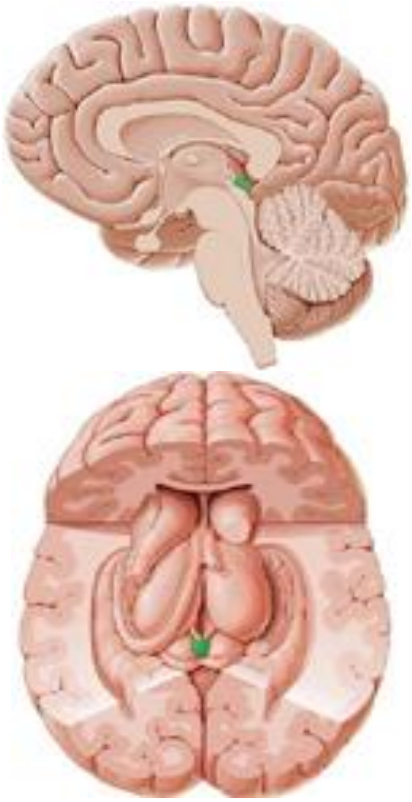
Pineal Gland Essentials-

- Of the endocrine organs, the function of the pineal gland was the last discovered.
- Located deep in the center of the brain, the pineal gland was once known as the "third eye."
- The pineal gland produces melatonin, which helps maintain circadian rhythm and regulate reproductive hormones.

A. Structure of Pineal Gland:

Anatomy

The **epiphysis cerebri** or **pineal gland** is a reddish-grey, approximately 5 – 8 mm long, pine cone-like structure that is located in the **diencephalic** part of the **prosencephalon** (forebrain). The gland was formed as an outward growth of the roof of the third ventricle. Therefore, the gland rests between the posterior aspects of the thalami as it projects posteriorly from the wall of the third ventricle.



Its attachment to either half of the brain is by the **Habenular commissure** and **trigone** superiorly, and the **posterior commissure** inferiorly. The Habenular and posterior commissures are a part of the pineal stalk. The Habenular commissure is a part of the **superior lamina** of the stalk, while the posterior commissure is a part of the **inferior lamina**. The space between the laminae is known as the **pineal recess**. It communicates anteriorly with the **hypothalamic sulcus** and the **third ventricle**.

It has two essential components one is hormone-producing cells called **Pinealocytes**, and the other is supporting cells that transmit information called **glial cells**.

The pineal gland often appears calcified in x-rays, which is usually due to fluoride, calcium, and phosphorus deposits that build up with age.

Histology

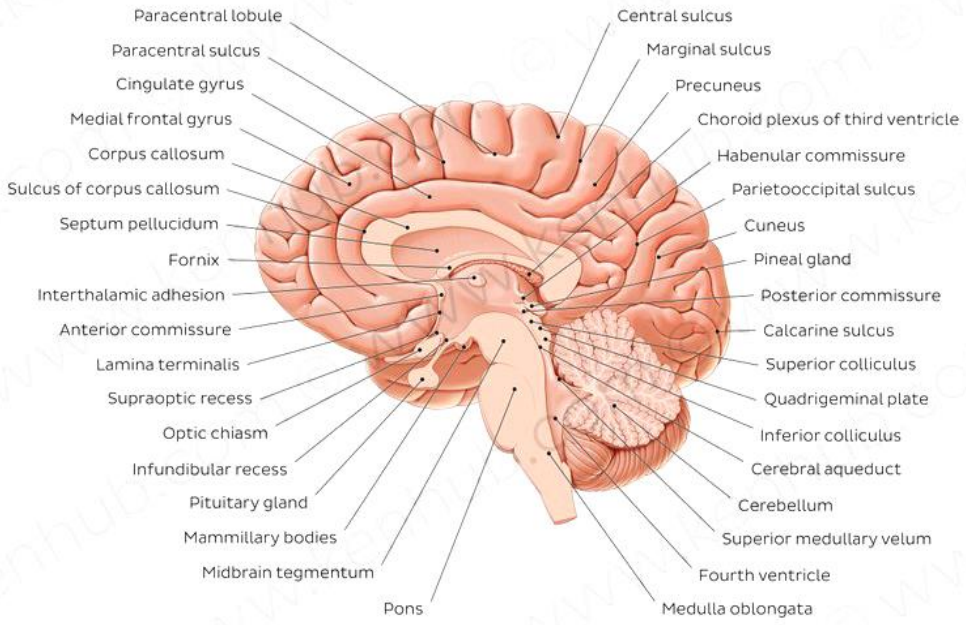
The pineal gland is encased by pia mater and lobulated by its connective tissue septae that projects into the gland. Within the epiphysis cerebri, there are **pinealocytes** and **neuroglia cells**.

The pinealocytes account for approximately 95% of the cellular content of the gland. They are irregularly shaped with peripheral processes, and lightly staining large round nuclei. Pinealocytes are primarily concerned with the photo-regulated production of melatonin. This hormone works with the body's circadian rhythm (which is controlled by the suprachiasmatic nucleus of the hypothalamus) to regulate the cycle of sleep and wakefulness. Additionally, some researchers believe that melatonin may alter sexual development in humans, contribute to thermoregulation, and cellular metabolism.

There are also the **corpora arenacea** (brain sand) bodies present within the gland. Calcification of these bodies is a common occurrence with increasing age. As a result, they appear as radiographic opacities on plain film radiography and can, therefore, be used as landmarks.

Vascular supply

Posterior medial choroidal artery provides the pineal gland with oxygenated blood and the **internal cerebral veins** drain deoxygenated blood from the pineal gland.



B. Secretion of Pineal Gland:

The pineal gland secretes a single hormone—melatonin (not to be confused with the pigment *melanin*). This simple hormone is special because its secretion is dictated by light. Researchers have determined that melatonin has two primary functions in humans—to help control your circadian (or biological) rhythm and regulate certain reproductive hormones.

C. Functions-

a) In Biological Rhythms:

Melatonin is a major natural hormone made in the mammalian pineal gland (Extrapineal tissues such as the retina, harderian glands, and gastrointestinal tract also synthesize the hormone but to a lesser extent). The melatonin-generating system is characterized by three basic features including **photosensitivity**, **diurnal (circadian) rhythmicity** (highest levels produced at night in darkness) and **age-related decrease in its activity**.

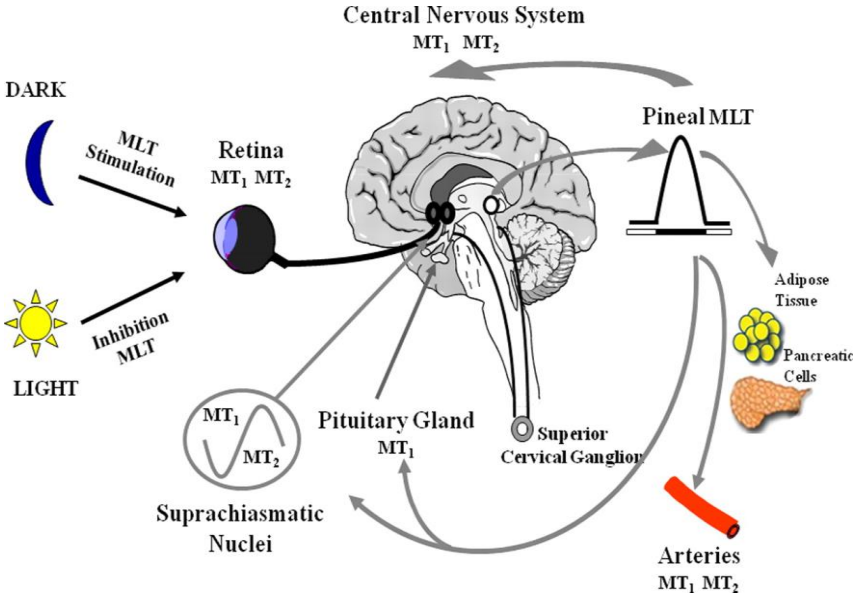
Before we start, let's have a look on sleep. Based on characteristic polysomnography signals, sleep has been divided into two distinct states known as rapid eye movement (REM) and non-rapid eye movement (NREM) that alternate in a periodic manner throughout the night. NREM sleep characterized by the presence of a minimum of 20% high voltage low frequency cortical δ waves (ranging from 0.5–2 Hz known as NREM 3) is also termed slow wave sleep (SWS) or deep sleep and provides an indication of the intensity or depth of sleep.

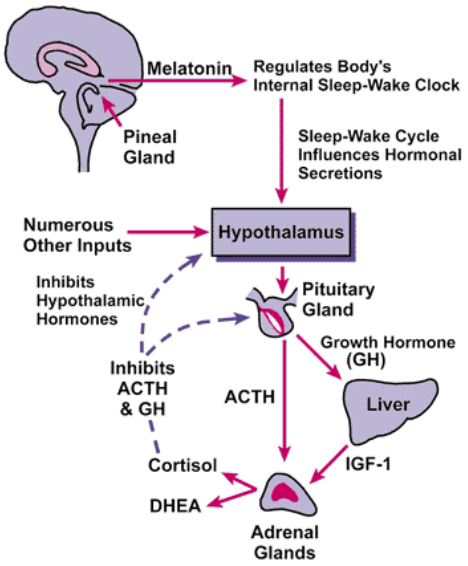
The circadian oscillator is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. It is the primary source of rhythmic temporal information (circadian pacemaker) for all physiologic processes including the modulations of sleep and wakefulness. The period, or frequency, of oscillation of the central circadian pacemaker is relatively insensitive to external and internal environmental influences.

Melatonin is an important physiological sleep regulator in diurnal species including humans. The sharp increase in sleep propensity at night usually occurs 2 h after the onset of endogenous melatonin production in humans; in addition, the duration of nocturnal melatonin relays night length information to the brain and various organs, including the SCN itself. The circadian melatonin rhythm is closely associated with the sleep rhythm in both normal and blind subjects. In humans and other diurnal species, melatonin acts at the SCN to attenuate the wake-promoting signal of the circadian clock, thus promoting sleep. In addition, melatonin acts at the default mode network (DMN) regions in the brain to promote fatigue and sleep-like changes in activation of the precuneus. The DMN is a network of brain regions that is active during rest in the absence of task-dependent performance. While asleep, connectivity within the DMN decreases and is diminished during SWS.

Melatonin has been reported to enhance sleep in rats, young chickens, and humans. In humans, for example, an intravenous bedtime dose of 50 mg reduced sleep latency, whereas three oral daytime doses of 80 mg enhanced sleepiness. On the other hand, no effect (except prolongation of REM sleep latency after the large dose) was reported following a 1 mg or 5 mg oral dose administrated at bedtime. Daily administration of 2 mg melatonin in the late afternoon induced unusual tiredness in the early evening after 4 to 5 days and an increase in plasma level that exceeded endogenous night time levels by a factor of 10 to 100. While it appears unlikely that melatonin is directly involved in sleep regulation, owing to the extremely large doses needed to alter sleep, it does appear that it may affect sleep indirectly by altering the phase of the circadian pacemaker. Melatonin may provide the first pharmacologic means of shifting the phase position of the circadian rhythm.

The production of melatonin generally decreases with age. Older subjects show an increased lag from sunset to the onset of melatonin pulse and to the melatonin pulse peak and between melatonin secretion peak and the middle of the sleep period. The apparent relationship between increasing age, declining melatonin production and increasing insomnia prevalence has led to the ‘melatonin replacement’ hypothesis, which suggests that replenishing the deficiency in the endogenous sleep-regulating hormone will improve sleep.





b) In Reproduction:

There's some evidence that light exposure and related melatonin levels may have an effect on a woman's menstrual cycle. Reduced amounts of melatonin may also play a role in the development of irregular menstrual cycles.

i) The effect of melatonin on the onset of puberty

It has been reported that melatonin secretion has an inhibitory influence on the hypothalamic secretion of GnRH in humans. It is therefore speculated that before puberty, melatonin concentrations are too high thus inhibiting the hypothalamic activation. But prior to puberty, the levels of melatonin decline below the threshold value thus forming the trigger signals of GnRH from the hypothalamus which leads to the onset of pubertal changes. Therefore, it is the decline of melatonin levels that trigger puberty. Studies have demonstrated that high nocturnal melatonin secretion in children delays puberty whereas low levels of melatonin have been shown to be associated with precocious puberty.

ii) The effect of melatonin in sexual maturation

Melatonin is involved in the control of pulsatile secretion of LH and that there is a negative correlation between nocturnal melatonin and LH concentrations. Furthermore, high levels of serum melatonin in women have been shown to be associated with amenorrhea accompanied with decreased GnRH/LH pulsatile secretion. Similarly, increases in nocturnal peak amplitude and duration of melatonin were reported in amenorrhoeic athletes who displayed irregularities in hypothalamic-pituitary-ovarian-axis functioning. *In vitro* studies have demonstrated that melatonin leads to the down-regulation of the *GnRH* gene expression in a cell line containing GnRH secreting neurons.

iii) The effect of melatonin on testicular function

In animal studies, it has been shown that melatonin may modulate testicular function. In mice and rats, it was reported that melatonin has an inhibitory effect on Leydig cells. The Leydig cells are responsible for the production of testosterone. Mel_{1a} and Mel_{1b} receptor mRNAs are expressed in epithelial cells of rat epididymis suggesting that melatonin has a role in the regulation of epididymal physiology. The epididymis is important for the maturation and storage of spermatozoa before they are ejaculated into the female reproductive tract.

It has been also reported that, long term administration of melatonin to healthy men is associated with decreased semen quality. Sperm concentration, motility as well as testosterone levels were found to be significantly decreased in healthy men administered with melatonin. On the other hand, an *in vitro* study demonstrated that administration of melatonin to human spermatozoa improved progressive motility and reduced the number of static cells.

iv) Effect of melatonin on ovary function

The melatonin is able to pass through all cell membranes and enter all tissues because of its lipophilic property, however, it specifically concentrates in the ovary. Studies have shown that high levels of melatonin are found in human preovulatory follicular fluid at concentrations which are much higher than those in serum. Larger the follicle the higher is melatonin concentration.

The ability of melatonin to promote embryo development in different species has correspondingly been reported. When mouse embryos were cultured in medium containing melatonin, increased blastocyst development rates were observed. This suggests that melatonin may be involved in embryo development.

Melatonin, secreted by the pineal gland, has been reported to be taken up into the follicular fluid from the blood. The free radicals produced within the follicles, especially during the ovulation process, are scavenged by melatonin, and reduced oxidative stress may be involved in oocyte maturation and embryo development. Evidence is pointing to the fact that melatonin treatment for infertility in women increases intra-follicular melatonin concentrations which subsequently reduces intra-follicular oxidative damage and elevates fertilization and pregnancy rates.