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Review Article

Pineal gland: A structural and functional enigma

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ABSTRACT

The structures and functions of neuroendocrine pineal gland remains an enigma to both philosophers and scientists alike since time immemorial. Some of the structural and functional mysteries of pineal gland are unfolded to some extent in this article by reviewing the work of various researchers. Recently a neuronal circuit consisting of seven neurons between retina and pineal gland have been established to relate the effect of light and other rays on its secretion.

The various physical properties such as piezoelectricity, piezoluminescence, electromagnetic field, solar flare, infrared energy are also explained and correlated with the structural and secretional components of the gland. The neurosecretion of pineal gland such as melatonin play an important role in sleep-wake patterns, timings and release of reproductive hormones along with temperature control.

The presence of all enzymes needed for the synthesis of di-methyl-tryptamine (DMT) in pineal gland explains the near death experience (NDE) phenomenon. The various audio-visual hallucinations in NDE phenomenon occur due to massive increase of DMT in pineal gland before death. A very high concentration of di-methyl-tryptamine (DMT), presence of retinal proteins in 5–10% of pinealocytes, its role in thermoregulation and a possible role as magnetoreceptor in blind men and highest deposits of fluoride in the body are not only interesting but significant for the future research. Hence a lot of further research on pineal gland is still required to correlate its unique properties with its structural components.

1. Introduction

The Pineal gland, a small piriform structure, shaped like cone of the pine tree, is located above and behind the hind brain (Fig. 1). The pineal gland for long has been regarded by the biologists as the vestigial organ, like vermiform appendix in the abdomen, with no functional importance and that it degenerates with age is well approved. However, in the religious texts, both in the eastern and western philosophies it has been regarded as the God organ, Pineal Eye, Third Eye, Eye of Shiva, Eye of Dangma, etc. The pineal gland's reference to being the "Third Eye" is quite ironic, as if, the gland has a lens, cornea and retina like actual eye. Galen named it as Konareion. Herophellus (c 300 BC) noted that pineal gland was the

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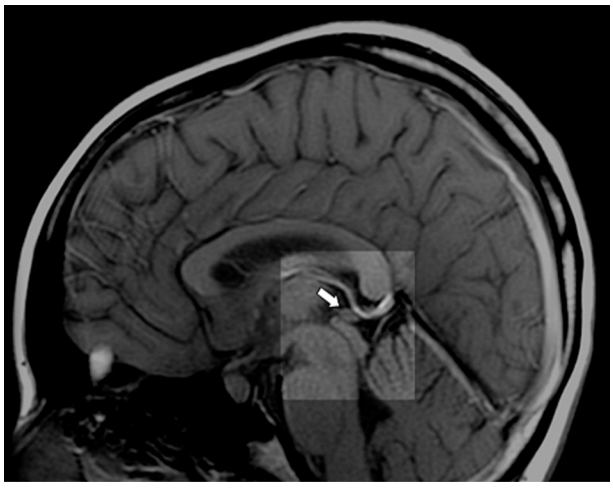

Fig. 1 – MRI of head in the lateral view showing the location of the pineal gland. Source: Frank Gaillard, in Radiopaedia.org. September 19, 2010.

first gland to develop around 3rd week of intra uterine life (IUL). René Descartes (1596–1650),[1] a French philosopher, physiologist, physicist, mathematician and natural scientist called it the "seat of the soul", intimately associated with the spiritual consciousness, intelligence etc.; this work was published in 1662.

It was not until the 1958 that scientists determined its function. Presence of photosensitive cells, synthesis of melatonin, regulatory control on all the major endocrine glands, modulation of sleep/wake patterns, seasonal functions[2,3] and circadian rhythm, etc., lead to a large number of researches on its developmental, histological, biochemical, evolutionary and functional aspects. It is now confirmed to be a neuroendocrine transducer of photic information into an endocrine response through the synthesis and release of the hormone melatonin. The pituitary gland which is regarded as the "master of the endocrine orchestra" is lieutenant of the pineal gland.

2. Structural aspects

Keeping the human head in the "Frankfurt plane" (lower border of orbit and upper margin of the external auditory meatus lie in one horizontal plane), it is situated about 12.00 cm behind and a little above the root of nose in the horizontal plane and about 5.00 cm deep to the skin and bone of head in a coronal plane (vertical plane) passing just behind the external acoustic meatus and about 5.00 cm above the opening of the external ear. The gland is reddish grey in colour, of the size of a rice grain, weighs a little above 0.1 g, measuring 7.0 mm in length, 5.0 mm in width (transverse) and 3.0 mm in thickness (vertical). The MRI study of 249 patients by Masayki Sumida et al (1996)[4] concluded that the size of pineal gland increased until the age of 2 years and thereafter remains stationary from 2 to 20 years of age. The gland is geometrically placed in the midline.[5] Due to mineral deposits that build up with age. The gland casts a radio-opaque shadow in the radiographs, CT and MRI images of brain/head which is a standard indicator of the midline position in the clinical practice.

The gland has a rich blood supply; only next to the kidneys. It is richly innervated by sympathetic and parasympathetic nerve fibres. *Sympathetic* fibres are derived from the T1 segment of the spinal cord. The nerve fibres enter from the dorsolateral aspect of the gland as the nervous conarii which may be single or paired. *Parasympathetic innervation* comes from the sphenopalatine and otic ganglia. In addition to above, the gland has *Central innervation* by some nerve fibres which penetrate the gland from the pineal stalk, which probably originate in the paraventricular nucleus of hypothalamus. Some neurons of trigeminal ganglia containing the neuropeptide- PACAP also innervate the gland.

With the evolution of the photoreceptor element in the pinealocyte cells, there has been a concomitant shift in the neural connection of the pineal organ. The pinealofugal, sensory innervation gave way to an autonomic, pinealopetal motor innervation. Thus, direct photosensitivity was superseded by indirect, optically-mediated control of the now secretory pineal gland. Pineal cytostructure seems to have evolutionary similarities to the retinal cells of chordates.[6] Avian pineal glands are believed to act like the Suprachiasmatic nucleus (SCN) in mammals.[7]

Microscopic examination in rats has revealed that the pinealocytes are structurally analogous to the retinal cones, lower order neurones and interstitial glial cells, indicating its possible original function as an organ of sight.[8,9] The development of cytoarchitecture reaches maturity by the middle of first decade.[4] The pineal gland consists of a capsule and the parenchyma. The parenchymal cells include: pinealocytes, peptidergic neuron-like cells, pineal neurones and neuroglia which includes the astrocytes, perivascular phagocyte, interstitial cells and vascular endothelium. The pinealocytes or chief cells (Fig. 2) account for about 95% of the cell population. The pinealocytes are both light and dark type.[10] Each cell has a polyhedral body and 4–6 long processes. They are highly modified neurons arranged as cords and clusters. About 5–10% pinealocytes have a selective group of retinal proteins.[11] The cell processes, 4 to 6 in number are long with expanded terminal buds. The buds end on the wall of the capillaries and on the ventricular ependyma of the pineal recess. Besides other organelles the terminal buds also contain polypeptide hormones, the monoamines and gama-aminobutyric acid which is a neurotransmitter. The major function of the pinealocytes is synthesis and secretion of the melatonin.[9]

Minute blood vessels enter the pineal gland through the trabeculae and form a network of fenestrated capillaries. They are closely related to the terminal buttons of the cell processes of pinealocytes. Various secretions of pinealocytes are discharged in the blood stream and also various amino acids and other substances required for the synthesis of pineal hormones etc., are taken up by the pinealocytes through this route. There are no blood-brain-barriers in the pineal gland.[12] The pineal gland is the locus of one of the circumventricular organs; the ependyma of the pineal recess is lined by modified ependymal cells, the tanycytes (tall, columnar, ciliated cells), for to and fro transport of neurochemicals in CSF.

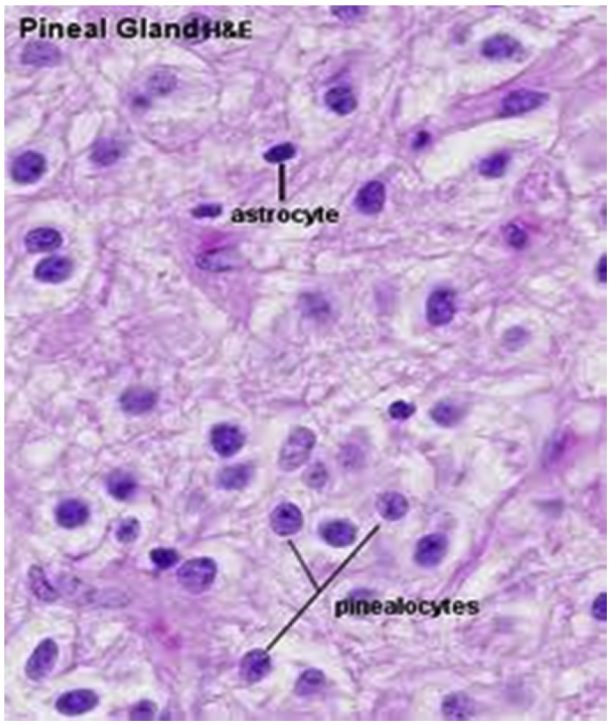

Fig. 2 – Histological picture of the pineal gland in high magnification (×100) showing Pinealocytes arranged in cords and blood capillaries. Source: www.Lab.anhb.uwa.au/school of Anatomy and Human Biology/The University of Western Australia.

The salts of calcium, magnesium, phosphorus, ammonium, aluminium and fluoride are found. These minerals are generally scattered in the extracellular matrix but often present as lamellated concentric calcareous deposits (Fig. 3)

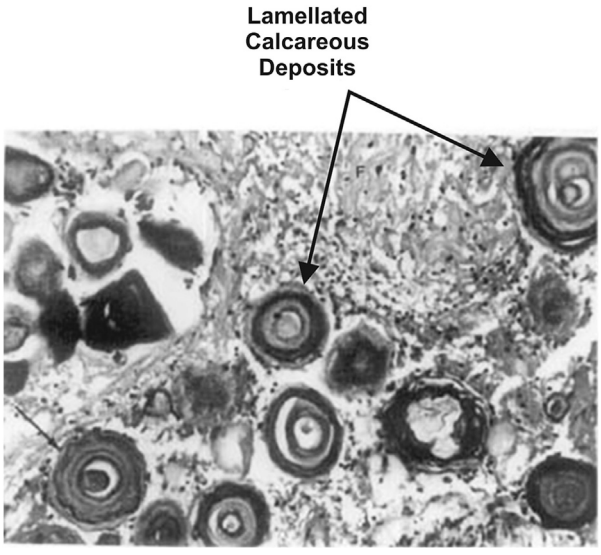

Fig. 3 – Histological picture of pineal parenchyma showing minerals present as lamellated concentric calcareous deposits known as corpora arenacea. Source: Koshy S and Vettivel SK, *J Anat Soc Ind* 50(1):1–6.

which are differently known as corpora arenacea, acervulus, psammoma bodies or brain sand.[13] They were earlier considered to be signs of ageing and degeneration. But Baconnier et al (2002)[14] described presence of calcite form of calcium carbonate in the normal pineal matrix.

Jennifer Luke (1997),[15] a British scientist, from the University of Surrey in England reported that the pineal gland is the prime target of the fluoride accumulation. Later her landmark study was substantiated by the similar reports.[16] Later it was discovered that the fluoride accumulation was strikingly high in the pineal gland.[17] In the same study Luke also reported that soft part (noncalcified) of the gland has a fluoride level of approximately 300 ppm while the hard part had a level of approximately 21,000 ppm. The magnetic forces attract the fluoride to the pineal gland. The impact of this accumulation is not yet fully understood. The available evidences suggest that the presence of fluoride reduces the melatonin levels and shortens the time to puberty.[15] Based on this and other evidences the National Research Council (USA) in 2006 declared that the fluoride is likely to cause decreased pineal function.[18] A new form of bio-mineralisation has been studied in the human pineal gland using Scanning Electron Microscopy (SEM) and Energy Dispersive Spectroscopy (Debbie Edwards).

The calcification of the pineal gland which is typical in adults has been reported in children as young as 2 years. The calcification occurs at any age[19]; but the amount of calcification is relatively independent of age.[20] There is microscopic evidence of an intimate association between the calcification and cellular membranes.[13] The calcified deposits are chemically similar to bone minerals[21] where they are known as hydroxyapatite crystals. The calcification rates vary widely from country to country, occurring in an estimated 40% of Americans by the age of 17 years.[5] Some recent studies have shown that the pineal calcification is significantly higher in Alzheimer's disease.[22] Researches suggest that the calcified deposits in the pineal gland are associated with decreased number of functioning pinealocytes and reduced melatonin production[23] as well as impairment in sleep-wake cycle.[24] The decline in melatonin has been suggested to be a trigger for the ageing process.

3. Functional aspects

Of various endocrine organs, the functions of the pineal gland were the last to be discovered. In the past any scientific enquiry of the Pineal gland was consciously avoided because of its association with various "Spiritual Phenomena". In 1917 it was known that the extract of cow pineal lightened the colour of frog skin. As yet the secretory activity of the gland is only partially understood. The functions of the gland are regulated by light and dark. The gland produces a number of hormones which are released both in blood and cerebrospinal-fluid (CSF). The release of secretions requires sympathetic stimulation. The known functions of the gland include:

- Synthesis and secretion of indolamines group of hormones viz., Melatonin, Serotonin, 5-Hydroxytriptamine, Norepinephrine and tryptophan.

- Synthesis and secretion of peptide group of hormones. These hormones exert inhibitory influence on the pituitary, thyroid, parathyroid, adrenal cortex, adrenal medulla, ovary, testis and endocrine pancreas.
- Synthesis of a psychoactive chemical di-methyl-tryptamine (DMT)
- Pinoline, present in significant amount in the pineal parenchyma is a betacarboline. It is a mono-amine oxidase (MAO) inhibitor called (6-methoxy tetrahydro betacarboline (6-Me OTHBC)) which acts on the GABA receptors. It is known to magnify and prolong DMT effects. Pinoline is a neuromodulator which prevents, amongst other effects, the breakdown of serotonin. Pinoline is superior to Melatonin in aiding DNA replication. Pinoline can make superconductive elements within the body. It encourages cell division by resonating with the very pulse of life - 8 cycles per second - the pulse DNA uses to replicate. This 8 Hz resonance was measured in healers by Andrea Puharich in the late 1970s.
- About 5–10% of the pinealocytes have a selective group of retinal proteins.[11] The lizard, frogs and birds use their pineal glands to detect light. In a paper published in the journal Neurochemical Research, RN Looley[25] wrote "… That the pinealocytes have a selective group of retinal proteins that are involved in the phototransduction cascade".
- The pineal is a thermoregulatory organ.[26] The temperature is up regulated by pineal gland and down regulated by the Suprachiasmatic nucleus.[27]

Aaron B Learner,[28] Professor of Dermatology and his coworkers at Yale University (U.S.A) hoping that a substance containing melatonin etc. from the pineal might be useful in treating skin diseases, isolated and named the hormone as melatonin in 1958 in a land mark research in Pineal physiology. Their work was later published in 1960. The pineal is the only gland in the body which converts serotonin into melatonin. The melatonin production starts by the age of 3rd month after birth and is inversely proportional to that of serotonin. The levels rise during darkness reaching a peak level of 300 pg/ml and fall during the day when the levels range from undetectable amount to 20 pg/ml. To an average the pineal gland produces <0.3 mg of melatonin per day. The period of usual onset and rise of nocturnal elevation of melatonin synthesis is not only sensitive to light but also to the effect of the magnetic fields.[29,30] The known melatonin mediated functions of Pineal gland include: regulating sleep-wake patterns, strengthens body immune system, regulates timing and release of female reproductive hormones, in females, regulates onset of menstrual cycle (menarche), cessation of menstrual cycles (menopause) and frequency & duration of menstrual cycle, a powerful antioxidant preventing cellular damage. Therefore melatonin has become popular in USA as the diet supplement, for lowering body temperature and heart rate, for strengthening body immune system, and to sense the direction (navigation tool) in blinds.

The abundant melatonin levels in the children are believed to inhibit the sexual development and the pineal tumours have been linked with precocious puberty. As the child reached closer to puberty the melatonin levels start falling. Similarly pinealectomy is known to result into precocious puberty.

The Suprachiasmatic nucleus (SCN) in the anterior hypothalamus uses a combination of daytime inhibitory and nighttime stimulatory signals to control the daily rhythm of pineal melatonin synthesis.[31,32] At night the sympathetic neurotransmitter norepinephrine (NE) is released from the postganglionic nerve terminals innervating the pineal gland, thus stimulating β1 and α1 adrenoreceptors on the pinealocytes.[33] The Melatonin also acts as a chronobiotic molecule,[34] stabilizing or re-enforcing the circadian rhythm of body functions in mammals like rodents.[35] The gland acts as an intrinsic time clock in the human body and regulates the circadian rhythm, evaluation of length of Day and Night, calculation of correct season to mate and turning up the sex drive. But many scientists believe that in the human beings the hypothalamus has taken this control and that the intrinsic rhythmicity of an endogenous circadian oscillator in the suprachiasmatic nucleus governs cyclical pineal behaviour.

There are a large number of environmental stresses which affect the pineal function, such as unusual light and dark rhythms, radiation, electromagnetic fields, sound, infrared radiations, nutritional imbalance, temperature swings, high altitude and over all daily stress.

Strassman (2001)[36] demonstrated synthesis of a psychoactive chemical di-methyl-tryptamine, DMT in the pineal gland. In an earlier study conducted by him[37] he proposed the theory that the DMT could be the "Spirit molecule". He hypothesised that there is a massive release of DMT from the pineal gland close to death and causes a near death experience (NDE), a phenomenon which is both auditory and/or visual. It was also demonstrated that DMT production is stimulated, in the extraordinary conditions of birth, sexual ecstasy, childbirth, extreme physical stress, near-death, and death, as well as meditation.[36]

4. Recent advances

4.1. *Neuronal circuits of pineal phototransduction*

The pineal gland has rich network of sympathetic, parasympathetic and some non-myelinated fibres from CNS and trigeminal ganglia.

In the human beings this neuronal circuit is multi neuron pathway. According to Standering (2008)[38] the 1st order neurons starts from the Glial cells (non-image forming cells) found in the 8th layer of retina. The light signals from the retina reach the suprachiasmatic nucleus (SCN) of the hypothalamus via retinohypothalamic tract. The 2nd order neurons carry the impulse to the reticular formation of brain stem. From there the 3rd order neurons descend as reticulospinal tract to the T-1 to T-3 spinal cord and end in the neurons of the lateral column. The 4th order neurons starting from the lateral column of T-1 come out from the ventral root of first thoracic spinal nerves (T1) and ascend in the cervical sympathetic chain to relay in the superior cervical ganglion. The 5th order neurons come out of this ganglion and ascend as a plexus around the internal carotid artery and its branches. The sympathetic nerve fibres finally leave the medial posterior choroidal arteries as nervous conarii to enter the

pineal gland from its posterior aspect. However, Singh (2006)[39] describe that the 5th order neurons in the nervous conarii enter the habenular nucleus and via habenulo-pineal tract. The 6th order neurons from the nucleus terminate in the ganglion conarii placed on the apex of the pineal gland and from there the fibres of the 7th order neurons enter the substance of the pineal gland.

Axelrod (1970) suggested an alternative neuron circuit and opined that the light signals reaching SCN travel via paraventricular nucleus (PVN) which relay the circadian signals to the spinal cord.[40] Thereafter these signals come out via sympathetic system to the superior cervical ganglia (SCG), and from there into the pineal gland. In the lower mammals the signals from the paraventricular nucleus reach directly to the Pineal gland via central innervation of the gland. However, in the human beings this path has not been reported so far.

4.2. *Piezoelectricity in the pineal gland*

Piezoelectricity is the electric charge that accumulates in certain solid materials, such as crystals, certain ceramics, bone,[41] DNA and various proteins in response to the applied mechanical stress.[42] The word piezoelectricity generally means electricity resulting from pressure. In the direct piezoelectric effect, an electric stress gives rise to voltage; in converse, an applied voltage results in the elastic strain. According to Cady (1964)[43] if the pineal calcifications were piezoelectric they could produce a surface charge distribution and a strain by virtue of the interaction of the direct and the converse piezoelectric effects whenever a subject was exposed to an appropriate electromagnetic (EM) radiation.

Published in the Bioelectromagnetics Journal, S.S. Baconnier (2002)[14] dissected 20 human pineal glands soon after death and reported 100 to 300, micro-crystals per cubic millimetre. He also observed that these micro-crystals were composed of a mineral called calcite. These crystals were hexagonal in shape, found floating inside the pineal glands and were very similar to the crystals found in the internal ear known as otoconia (otolith crystals). These crystals consist of calcium, carbon and oxygen; expand and contract due to the presence of electromagnetic fields converting it into photons. David Wilcock[44] in his book The Source Field Investigations mentioned that the calcite micro-crystals could be responsible for an electromechanical biological transduction mechanism in the pineal gland, due to their structure and piezoelectric properties. Way back in 1957 Nye,[45] with the help of the results of second harmonic generation (SHG), demonstrated that the pineal gland contained noncentrosymmetric material which according to the crystallography symmetry considerations is piezoelectric. A positive SHG response in his study was a proof of the presence of piezoelectric crystals.

In a significant multicentric study Sidney B. Lang with his co-workers (1996)[16] from Israel and USA working on the pineal gland of cadavers demonstrated that the piezoelectric crystals were detected throughout the pineal gland; the distribution and size of the crystals considerably varied. The hard part of the gland, however, possessed hydroxyapatite crystals. They identified three classes of crystals in the pineal parenchyma (a) mulberry-like, (b) non mulberry-like and (c) non calcium containing crystals.

The classical methods for measuring piezoelectricity[43,46] are not suitable for examination of specimens containing small piezoelectric crystals dispersed in the nonpiezoelectric material therefore an alternative technique that would detect noncentrosymmetry—Second Harmonic Generation (SHG)[16] as suggested by Dougherty and Kurtz (1976)[47] and Kurtz and Dougherty (1978).[48]

It has been observed that the piezoelectric property in calcite micro-crystals is in the frequency range of mobile communications. These crystals are capable of tuning into radio stations without the use of electricity. Piezoelectric crystals are used to turn sound vibrations into electrical current. The researches have shown that the cell phone use and other microwave emitting devices have an adverse effect on the pineal gland by changing the way piezoelectric crystals in human pineal gland function by interrupting the synthesises the melatonin.

The presence of calcite micro-crystals, their contraction and expansion in the presence of electromagnetic field and piezoelectric property may go well with the hypothesis of Gottfried de Purucker (2011)[49] published in the book 'Man in Evolution' in which the author mentions that "*whenever we have a hunch, the pineal gland is vibrating gently; when we have an intuition, or an inspiration, or a sudden flash of intuitive understanding, it vibrates more strongly though still gently.*"

4.3. *Piezoluminescence and the pineal gland*

The piezoluminescence is emission of light created by pressure upon certain solids. According to Atari (1982)[50] it is characterised by recombination of processes involving electrons, holes and impurity ion centres. The calcite microcrystals in the pineal gland give off light; the phenomenon is known as piezoluminescence. The light produced is a cold light viz., light without heat, ranging in the blue-green light spectrum. A similar phenomenon occurs in certain marine animals in the deep sea and some insects. The DMT and tryptophan, found in high concentration in the human pineal also have piezoluminescent qualities.[51] The classical picture depicting the pineal gland as the centre for spiritual and psychic energy and piezoluminescence is most widely used in most of the monographs on pineal gland.

4.4. *Electromagnetic field and the pineal gland*

The human beings are surrounded by 60 Hz electrical fields in our homes, work and outside where power lines tower over almost every street.[52] The electromagnetic field (EMF) suppresses the activity of the pineal gland and reduces the melatonin production, but the process which converts the electromagnetic signals to chemical ones which regulate melatonin synthesising gene regulation is not known.[42] James et al, (1999)[52] opined that there is no escape from this except to flee to a remote place, discretely or unpopulated area. But even there the pineal gland could be under siege.

The pineal gland contains magnetic material in birds and other mammals. In birds the gland, being magnetorecepter helps to align the body in space. It works as centre for navigation which may be the case in blind men too.

In a significant study conducted on 7 male volunteers (aged 16–22 years) at the University of Dortmund, West Germany, Grieffahn et al, (2002)[53] observed that different parts of the electromagnetic spectrum (a) moderate bright light, (b) very strong magnetic field and (c) Infrared radiation suppress, at least partially, melatonin synthesis.

4.5. *Solar flares and the pineal gland*

Richard Carrington[54] observed a solar flare for the first time on 1 September 1859 projecting the image produced by an optical telescope, without filters Fig. 4. These flares keep happening very now and then in varying quantum and frequencies. These flares produce radiation across the electromagnetic spectrum. According to a study published in the New Scientist back in 1998, there is a direct connection between the Sun's solar storms and human biological effects. These flares use the same conduit to reach the earth as is used for the ordinary solar radiations. Pineal gland in our brain is stimulated by the increased electromagnetic activity during the solar flare which causes the gland to produce excess melatonin.

4.6. *Infrared energy and the pineal gland*

Infrared energy waves, the lower frequency waves on the light spectrum have longer wave length. They correspond with lower emotional energies and moods. While the higher frequency energy waves such as green, blue and violet range produces higher emotional energies and moods. Result of strong pulses of infrared energy waves on the brain and especially the calcite micro-crystals in the pineal gland are (a) Sleepiness, (b) Crying, (c) Agitation, (d) Depression, (e) Anxiety, (f) Aggression, (g) Fear, (h) Terror, (i) Hopelessness, (j) Grief, (k) Apathy and (l) Even death.

Studies on rodents[55] suggest that the pineal gland may influence the actions of recreational drugs, such as cocaine and antidepressants, such as fluoxetine.[56]

Fig. 4 – A photograph of Solar Flare Source: http://portlandmaineacupuncture.com/the-effect-of-solar-flares-on-our-pineal-gland/.

4.7. *Pineal gland and circadian rhythm*

In the human beings the cells of retina, iris, skin and pinealocytes possess light-sensing capabilities. When these cells are cultured, they mark out an independent rhythm. It is the role of the pineal gland and the hypothalamus to unite and manage them correctly—like a control tower for the biological clock.

Pinealectomy is reported to block photoperiodic responses in all experimental mammals.[57] Surgical pinealectomy in rats housed under a 12:12 light–dark cycle did not affect REM or NREM[58] .In another study it was observed that although the pinealectomised rats housed in constant darkness exhibited a decrease in the amplitude of the circadian rhythm of REM and NREM sleep.[59]

In the retina of hamsters there is another centre for melatonin metabolism indicating that the eyes have their own built in circadian rhythm. The researchers are looking for exact location of this clock in the human eye. They demonstrated that the retinal clock could be set and reset even when the SCN was destroyed. No one yet knows what this separate clock is for or how it regulates the SCN.

5. Conclusions

Based on the review of structural and functional aspects (piezoelectric, piezoluminescent and other electromagnetic properties) of the Pineal Gland it is concluded that:

- The gland is light sensitive and the phototransduction path is multi neuronal.
- The pineal hormones are up regulated in the dark and down regulated in the light.
- The pineal hormones regulate pituitary, thyroid, parathyroid, adrenal, ovary, testis, and endocrine pancreas. The gland is thermoregulatory; regulates the sleep wake cycles and sex pattern too.
- Though it regulates the circadian rhythm in the lower mammals but the same is doubtful in the human beings.
- The presence of retinal proteins, its evolutionary closeness to the retina, presence of a separate circadian rhythm in the retina, piezoelectric and piezoluminescent crystals in the gland, sensitivity of pineal to the electromagnetic forces, magnetoreceptor properties and its possible role as an instrument of navigation in the blinds are interesting and need further probe.

Conflicts of interest

All authors have none to declare.

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