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Review Article

Updating the Pineal Gland Mystery: Purpose and Function in Children and Adult Health and Pathology

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Abstract

The human pineal gland is considered as a "type A" organ, meaning it lies proximal to the third ventricle. It is principally comprised of two cell types: pinealocytes, which make up most of the gland (85–90%), and glial cells (mostly astrocytes). The gland is relatively small in < 2-year-old children. Moreover, its size does not significantly change between 2–20 years of age. The pineal gland is a neuroendocrine organ that secretes the hormone melatonin. The pineal body is thusly implicated in pigmentation, reproductive organ functions, seasonal breeding, and jet lag. It is also referred to as a "biological clock" [10] that plays a crucial role in regulating the circadian rhythm in humans. The pineal gland also produces N, N-dimethyl-tryptamine (DMT), that is found in certain plants and acts as a hallucinogen. The pineal gland is aptly called a neuroendocrine transducer as it converts the neuronal signals into hormones, affecting various physiological functions and conditions of an organism.

Calcification (calcium deposits) is a landmark feature of the pineal gland on x-ray and magnetic resonance imaging (MRI). The degree of calcification depends on age and is usually very high in individuals older than 30 years. Calcification is typically caused by the deposition of hydroxyapatite, leading to reduced melatonin secretion. Pineal calcification has been implicated in Alzheimer's disease. Pinealectomy is the surgical removal of the pineal gland for medical reasons. However, only a few studies have investigated the effect of pinealectomy on humans. Studies on the pineal gland have been aimed at determining its effects on human physiological processes and those of other organisms. The presence of melatonin from the protozoa to highly evolved mammals indicates the gland's significance. Thus, it is imperative to gain further insights into and understanding of this gland and its hormones to uncover more practical therapeutic and preventive options.

Dysregulation of melatonin secretion can occur in several pathophysiological conditions. In scoliosis, the spine curves abnormally toward one side. Currently, there is insufficient evidence to confirm the relationship of melatonin in adolescent idiopathic scoliosis, although it is being considered. In humans, melatonin facilitates osteoblast (cell) differentiation. Pineal gland tumors have been rarely reported. However, pineoblastoma and pineocytoma have been observed in adults. Pineal-origin breast cancer seldom occurs unless a pineal tumor metastasizes to distinct tissues and organs, such as breast tissue.

For this reason, the pineal gland is sometimes referred to as the oncostatic structure in the brain. Children with autism spectrum disorder (ASD) commonly experience insomnia and display behavioral problems. Notably, clinical studies have suggested a direct association between ASD and diminished melatonin levels.

This review investigates and summarizes pineal gland purpose and function in humans, and hopefully helps decipher the great "mystery" surrounding this relatively small but significant gland.

Keywords: *Alzheimer's Disease; Autism; Breast Cancer; Calcification; Circadian Rhythm; DMT; Melatonin; Scoliosis*

Abbreviations

AANAT: Arylalkylamine N Acetyltransferase; AIS: Adolescent Idiopathic Scoliosis; ASD: Autism Spectrum Disorder; CSF: Cerebral Spinal Fluid; CVO: Circumventricular Organ; DMT: N, N-Dimethyl-Tryptamine; GPCR: G-Protein Coupled Receptor; HPLC: High-Performance Liquid Chromatography; PRC: Phase-Response Curve; PVN: Paraventricular Nucleus; REM: Rapid Eye Movement; SCG: Superior Cervical Ganglia; SCN: Suprachiasmatic Nucleus

Introduction

Research on the pineal gland or epiphysis cerebri, a neuroendocrine transducer, has been receiving considerable attention, but its function in humans remains unclear [1]. It is a small gland measuring only 5–9 mm in length [2]. The term pineal is derived from the Latin word "*pinea*" meaning "pinecone".

The pineal gland anatomy was first illustrated centuries ago. The first scientific documentation of this gland can be found in the *8th Book of Galen* (written circa 130–210 CE by Greek physician and philosopher Aelius Galenus or Claudius Galenus). Galen's (the name's Anglicize version of the name) description of the gland was incorrect from the standpoint of modern medicine, but paved the way to a better understanding of its anatomy. There are several text descriptions of the pineal body, and notable among them is that of René Descartes (1596–1650), a French scientist, philosopher, and mathematician. According to Descartes, the movement of the pineal body contributes to specific bodily actions, and the small gland also serves as a *sensus communis*, a part of the brain concerned with sense [3]. Most of Descartes' views and writings were not supported by physicians of later dates. Much of the relevant scientific studies conducted in the 20th century contributed significantly to understanding this enigmatic organ [3]. Immense curiosity among scientists was generated when the pineal body was determined to be an endocrine gland [4].

Discussion

The pineal gland is considered a neuroendocrine organ that secretes the hormone melatonin [5]. The pineal body is, therefore, implicated in pigmentation [6], reproductive organ functions [7], seasonal breeding [8], and jet lag [9]. It is referred to as a "biological clock" [10] as it is fundamentally involved in regulating the circadian rhythm in humans. Melatonin is called the "hormone of darkness" [11]—its secretion is induced by darkness and inhibited by natural day or artificial light [12]. The pineal gland also produces N, N-dimethyl-tryptamine (DMT)—found in specific plants, and acts as a hallucinogen. However, there is no scientific evidence if it induces human endogenous DMT-psychedelic responses [13].

The pineal gland is suitably referred to as a neuroendocrine transducer [1] as it converts neuronal signals into a hormones that affect various physiological states of an organism.

Origin and location

A member of the circumventricular organs (CVOs) [14], the pineal gland is deeply seated in the human brain. Oksche (1965) conducted fate-map studies (refer to Supplementary Note 1 at the end of this review). Oksche reported that the embryological development of the rat pineal gland begins as an evagination in the middorsal region of the diencephalon, but is later shifted to the posterior region due to tissue movement [15]. However, in humans, this azygous gland is derived from the posterior region of the roof plate of the third ventricle during the 6th week of development [16].

Morphology

According to Vollrath (1981), the human pineal gland is classified as a "type A" organ, meaning that it lies proximal to the third ventricle [17]. This reddish-gray tiny gland weighs less than 200 mg. It is primarily composed of 2 cell types: pinealocytes (that comprise 80–90%

of the glandular structure) and the gland (85–90%), and glial cells (mostly astrocytes) [18]. The gland is richly supplied with blood vessels—with a blood flow rate of 4 mL/min/g. The pineal melatonin is transported to the blood capillaries and cerebral spinal fluid (CSF) through pineal recess as soon as it is produced in the pinealocytes [19]. Similar to other CVOs, the pineal gland lacks a blood-brain barrier [20].

The human pineal gland size varies with age [21]. A magnetic resonance imaging (MRI) study by Sumida., *et al*. (1996) revealed that the gland size to be minimal in <2-year-old children. However, its size does not significantly change between 2 and 20 years of age [22]. They are absent in certain tropical animals and enlarged in several high-altitude species [23].

Calcification (calcium deposits) is a landmark feature of the pineal gland on x-ray and MRI. The degree of calcification depends on age and is characteristically elevated in individuals older than 30 years [24]. Calcification is caused by the deposition of hydroxyapatite, leading to reduced melatonin secretion. Pineal calcification has also been implicated in Alzheimer's disease [25].

Physiology

As mentioned earlier, the pineal gland plays a significant role in regulating the human biological clock. The light signal is captured and transmitted to the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract (RHT), and then relayed to the paraventricular nucleus (PVN) and subsequently to the superior cervical ganglia (SCG).

The pineal gland is innervated by postganglionic sympathetic nerves arising from the SCG that releases the neurotransmitter noradrenaline [19]. Pinealocytes display alpha and beta noradrenergic receptors [20]. Noradrenaline stimulates the pinealocytes to form melatonin. Hence, vast neuronal network participates in forming the hormone that is vital for regulating the circadian rhythm in humans. The SCN has melatonin receptors that follow a feedback mechanism to regulate the release of melatonin in the pinealocytes [20].

Pinealocytes uptake tryptophan, an essential aromatic amino acid, through the bloodstream. In the presence of noradrenaline, the tryptophan undergoes metabolic changes to form serotonin and, ultimately, melatonin. The production of melatonin by pinealocytes is catalyzed by various enzymes, among which the rate-limiting arylalkylamine N acetyltransferase (AANAT) is the most significant [26].

The SCN is a circadian pacemaker activated via the RHT arising from the retina [19]. The RHT is found in most mammals, including humans. Melatonin biosynthesis is increased during the dark and released into the CSF and blood [27].

Melatonin serves both as a hormone and natural antioxidant [28]. Like other hormones, melatonin acts through its MT1 and MT2 (MTNR1A and MTNR1B in humans) receptors [27]. These receptors are present in various parts of the brain, including the cerebellum [29], hypothalamus [30], pituitary [30], retina [31], and SCN [30]. It is also present in other cells and organs, such as lymphocytes [32], kidneys [33], granulosa cells [34], and pancreatic islet cells [35].

The genes for MTNR1A and MTNR1B are located in chromosomes 4 and 11, respectively. The receptors are 351- and 363-amino acid-long transmembrane proteins with well-conserved intracellular and extracellular loops [36]. They belong to the superfamily of G-protein coupled receptors (GPCRs) that bind to melatonin, bringing about a regulatory change in cell functioning by inhibiting the production of cAMP and protein kinase A [37]. The binding of these receptors to melatonin enables the regulation of various clock genes and clock-controlled genes through a cascade of reactions in the signal transduction pathway. This process is also called the "prospective effect" of melatonin [27].

Melatonin secreted by cells other than pinealocytes is not detected in the serum. Radioimmunoassay and high-performance liquid chromatography (HPLC) are used to determine melatonin levels in the serum, saliva, and urine [9,38]. Serum concentrations of melatonin range from < 20 pg/mL during the day to 100 pg/mL at night [9]. Regulation of the circadian clock by melatonin can be visualized by plotting phase-response curve (PRC). As such, (PRC)—(refer to Supplementary Note 2 at the end of this review). PRC data can drive the diagnosis and treatment of disorders related to melatonin secretion [20].

The pineal gland acts as a photoreceptor in lower vertebrates, such as lampreys and specific cold-blooded vertebrates (being fish and amphibians) [39]. However, the gland functions are restricted to hormone secretion in highly evolved vertebrates, including mammals [9].

Functions

Independent studies by Fiske (1960) provided early insights into the functioning of the mammalian pineal gland. Fiske reported the gonad enlargement and decreased pineal gland weight in rats exposed to constant illumination [40]. These experiments revealed the possible involvement of the gland in the reproductive regulation of organisms utilizing light (day) signals from the environment. The pineal gland is extremely small or completely absent in many vertebrates [23]. Some, warm-blooded organisms, such as birds and mammals, are reported to survive a pinealectomy [41,42].

Hydroxyl and peroxynitrite, the most reactive free radicals generated intracellularly, are effectively neutralized by melatonin [44]. The hormone also helps scavenge other radicals, such as hydrogen peroxide, nitric oxide, and hypochlorous acid by stimulating the antioxidant enzymes superoxide dismutase, glutathione peroxidase, and catalase [43]. Melatonin is also found in bacteria, especially photosynthetic cyanobacteria where it primarily acts as an antioxidant [28].

Lynch., *et al* (1975) was one of the first research groups to investigate the human melatonin rhythm. They measured the melatonin level in human urine samples. They found high levels of the hormone in the urine samples collected during the night compared to those collected during the day [45].

Developmental studies have shown that melatonin increases during a human fetus' gestation period as the placenta allows maternal melatonin to enter the fetus' bloodstream. The entry of maternal melatonin into the fetus' neuroendocrine system helps the newborn adjust to the circadian rhythm [9]. Melatonin levels increase continuously from birth to adolescence, and noticeably decreasing during the post-pubertal stage [46]. The hormone levels do not fluctuate considerably during the third to fourth decades of life, but decline steadily thereafter. This pineal gland size decrease gland size is deemed to affect the aging process [20].

Recently, it has been revealed that the plasma membrane glucose transporters GLUT/SLC2A facilitate the movement of melatonin inside specific cells [38]. Classical studies have determined a relationship between glucose and the pineal gland. Many studies have specifically linked pineal melatonin with insulin in mammals. It is suggested that diminished pineal melatonin results in increased insulin production from the pancreas [38]. These studies provide support for future clinical investigations into discovering effective therapies for diabetes.

Conditions and disorders

The dysregulation of melatonin secretion may result in various pathophysiological conditions. Healthy levels of melatonin regulation and secretion are vital, owing to a human's physiological adaptations in response to environmental cues [20].

Pineal gland's role in the maintenance of the biological clock

As previously stated, melatonin secreted by the pineal gland [5] acts as a neuroendocrine transducer by converting exogenous light signals into endogenous chemical hormones that can profoundly affect an organism's physiology [20]. Light cues received by the retina are transmitted to the SCN; the SCN then conveys the signal to the pineal gland through a multisynaptic pathway in which the PVN performs an intermediary function [19].

Several studies have reported on melatonin's role internal biological clock regulation. Sleep is essential to maintain homeostasis and improve cognitive functions [47]. Hence, a sleep-wake cycle disruption can lead to behavioral changes. In one study, oral supplementation

of melatonin shifted human cicadian rhythym. The rhythms were delayed if melatonin was administered in the morning and advanced when administered in the evening—as recorded using a PRC. The findings emphasized melatonin's significant adverse impact on the sleep-wake cycle in humans [48]. This study also explained the behavioral patterns of shift workers and the phenomenon of jet lag [48].

Zisapel., *et al*. (2001) reported on melatonin levels during the daytime and nighttime human sleep patterns. Clinical supplementation of the sleep-regulating hormone could induce sleep in night shift workers and alleviate sleep disorders, including age-related insomnia [49]. A combination of melatonin and light therapy has also been suggested for treating sleep disorders [50]. The use of melatonin to treat sleep disorders has been justified by several studies [51]. Melatonin can also help allay jet lag—cause by traveling to different time zones and causing, making the body's circadian clock to unsync [52].

The effect of jet lag is more pronounced if the distance traveled by an individual is more and in the eastward direction. Melatonin administration can significantly reduce jet lag; an oral dose of 3–5 mg may advance the circadian lag by 1–1.5h [52].

Role of the pineal gland during puberty

In humans, adolescence or puberty is a stage of attaining sexual maturity. Secondary sexual characteristics are developed during this stage. Typically, the onset of puberty is age 10–11 in girls and 11–12 in boys [53]. If the puberty process commences before the mean age, it is termed precocious puberty. Only a limited number of human clinical research studies have been conducted regarding the effects of melatonin in puberty [54].

In another clinical experiment, Salti., *et al*. (2000) assessed melatonin levels in blood samples obtained at night from 8 boys and 8 girls in the Tanner pubertal stage. Melatonin secretion was found to be associated with the pubertal stage rather than the expected growth stage. Also, melatonin sevretion decreased post-adolescence. The researchers further noted a possible connection of melatonin levels with rapid eye movement (REM) [55].

Role of the pineal gland in scoliosis

In scoliosis, the spine curves abnormally toward one side. Currently, there is very little evidence supporting melatonin involvement in adolescent idiopathic scoliosis (AIS). Studies conducted on birds and mammals other than humans have indicated that melatonin improves bone quality [56,57]. A human *in vitro* study revealed that melatonin facilitates the differentiation of osteoblast cells [58].

Pineal gland's role in cancer and immune system

Pineal tumor

Pineal gland tumors are rarely reported. A classification of the pineal tumors by Gheban., *et al*. (2019) revealed that pineoblastoma, an ill-differentiated tumor, is more commonly noted in children, while pineocytoma, a well-differentiated tumor, is more often observed in adults [2].

Breast cancer

Generally, every cell in a multicellular organism has cell-cycle checkpoints at which cell divisions are regulated. Sometimes, the cell loses the "regulatory switch" of these checkpoints and undergoes uncontrolled divisions, leading to tumor development. Tumor cells can metastasize to other tissues and organs. Regarding such, the pineal gland is sometimes referred to as the oncostatic structure in the brain [59].

Individuals working in night shifts are exposed to artificial light, reducing their melatonin levels [60]. In an earlier study by Cohen.,

et al. (1978), decreased melatonin secretion by the pineal gland was supposed to be responsible for the induction of breast cancer. This hypothesis was based on the observation that melatonin influences ovarian estrogen production—increased estrogen level has been reported in patients with breast cancer [61].

Another study demonstrated the antimitotic effects of melatonin. Breast cancer cells stopped dividing in the presence of melatonin under *in vitro* conditions. This study was significant because it demonstrated that melatonin influences the p53 (a tumor-suppressor gene), pathway [62].

Other cancers

Alterations in melatonin secretion have also been implicated in other cancers. *In vitro* studies have unraveled the antiproliferative effects of melatonin in human ovarian carcinoma cells [7], endometrial adenocarcinoma cells [63], and uveal melanoma cells [64]. The oncostatic actions of melatonin were also reported regarding intestinal tumors in rats [65]. The melatonin receptor, MT2, expression was reported to be decreased in metastasized cancers. The finding suggested the possible protective action of melatonin against uncontrolled cell proliferation [66].

Melatonin has been shown to shield cells from the toxic effects of radiotherapy and chemotherapeutic drugs. Clinical studies have reported the beneficial effects of melatonin in treating several human cancers—which is understandable in that melatonin acts as an antioxidant and an oncostatic agent. Thus, in summary, numerous studies have noted the use of melatonin to treat various human cancers [67].

Clinical evidence is needed to quantify the physiological doses of exogenous melatonin for the treatment of various disorders. As a footnote, melatonin catabolism primarily occurs in the liver [27].

Autism

Children with autism spectrum disorder (ASD) generally experience insomnia. Also, these children demonstrate behavioral problems. Clinical studies have suggested a direct correlation between ASD and diminished melatonin levels [68]. A clinical trial was conducted on children aged 3–10 years diagnosed with ASD and sleep disorders. These children were given melatonin supplements. The research team monitored the subject children's sleep pattern and assessed the melatonin levels in the blood serum of these children. The team reported improved levels of sleep and an almost average level of melatonin in their blood serum. The findings indicated need to include melatonin as a possible treatment approach for ASD patients [50].

Pinealectomy

Pinealectomy is the surgical removal of the pineal gland for medical reasons. As previously discussed, pineal melatonin is a critical chronobiological factor in maintaining a healthy sleep-wake cycle. Very few studies have investigated the effects of pinealectomy in humans. Nevertheless, in one case study, patients who underwent pinealectomy experienced hyper-insomnia [42]. In another study reported the effect of pinealectomy in patients with pineocytoma. Patients in the study experienced sleep disturbances after pinealectomy were noted [69].

Simko., *et al*. (2013) wrote that melatonin deficiency in experimental animals was achieved by either removing the pineal gland or keeping the animals under constant illumination. The study reported a decreased level of nocturnal melatonin, leading to high blood pressure in human subjects. Decreased melatonin levels adversely affect the functions of the heart, kidneys, and circulatory system. These data suggest that melatonin helps reduce hypertension and regulate the physiological functions of other human organs. Melatonin is occassionally used for the treatment of high blood pressure [70].

Conclusion

The pineal gland is considered a neuroendocrine organ that secretes the hormone melatonin. Thus, the pineal body is implicated in pigmentation, reproductive organ functions, seasonal breeding, and jet lag. It is also referred to as a "biological clock" [10] as it plays a vital role in regulating the circadian rhythm in humans. The pineal gland secretes N, N-dimethyl-tryptamine, found in certain plants and acts as a hallucinogen. It is aptly called a neuroendocrine transducer as it converts neuronal signals into hormones, affecting various physiological physiological of an organism.

The human pineal gland is classified as a "type A" organ, meaning it lies proximal to the third ventricle. It is primarily composed of two cell types: pinealocytes, which make up most of the gland (85– 90%), and glial cells (predominantly astrocytes). The gland size is minimal in < 2-year-old children, and its size does not significantly change between 2–20 years of age.

Calcium deposits (calcification) are identifiable features of the pineal gland on x-rays and MRIs. The calcification degree depends on age and is typically quite pronounced in individuals older than 30 years. Calcification is commonly caused by the deposition of hydroxyapatite, leading to reduced melatonin secretion. Pineal calcification has been implicated in Alzheimer's disease.

Melatonin secretion dysregulation can result in various pathophysiological conditions. Currently, there is very little evidence to support the association of melatonin in adolescent idiopathic scoliosis, although it is being considered. In humans, melatonin facilitates the differentiation of osteoblast cells. Pineal gland tumors are infrequently reported. However, pineoblastoma and pineocytoma have been seen in adults. Pineal-origin breast cancer seldom develops unless a pineal tumor metastasizes to other tissues and organs, such as breast tissue.

For this reason, the pineal gland is sometimes mentioned to as the oncostatic structure in the brain. Children with autism spectrum disorder widely experience insomnia and elicit behavioral issues. Remarkably, clinical studies have inferred a direct correlation between ASD and diminished melatonin levels.

Pinealectomy is the surgical removal of the pineal gland for medical reasons. However, only a few studies have investigated pinealectomy's effect on humans. Studies on the pineal gland have strived to ascertain its influences on the physiological processes in humans and other organisms. The presence of melatonin from protozoa to highly evolved mammals reveals the gland's significance. Thus, it is compelling to gain further insights and conclusions regarding this gland and its hormones to investigate and develop more effective therapeutic and preventive treatment choices.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Supplementary Note 1

According to Legué and Joyner (2010): "Fate mapping techniques are fundamental to studying cell behaviors such as proliferation, movement, and lineage segregation, as the techniques allow precursor cells to be marked and their descendants followed and characterized over time" [71].

Supplementary Note 2

According to Hastings and Sweeney (1958), DeCoursey (1961), and Winfree (1980): "The phase response curve (PRC) expresses the magnitude and direction of the phase shift as a function of the time that the stimulus is given" [72].

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