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The Pineal Gland, A Bridge Between the Hormonal Perspective and Spiritual Mysticism

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ABSTRACT: The pineal gland has a hormonal and mystical component, described since time immemorial; its main secretion product with recognized health effects is melatonin, which is involved in the light/dark phenomenon. Additionally, this gland has been related to spiritual aspects and divine connection; in fact, for certain traditions, they define it as the "Third Eye" and establish it as the link between the "Body and Mind".

This review describes the most relevant aspects of the functioning of the pineal gland (from a hormonal point of view) and its possible role from a mystical-spiritual point of view.

KEYWORDS: Pineal, Gland, Melatonin, Chakra, Spiritual.

INTRODUCTION

Descriptions of the pineal gland date back to ancient times, but many of its functions are still not fully known. In vertebrates with diurnal and/or nocturnal activity, its main product, melatonin, is synthesized and secreted in a rhythmic pattern (in the presence of darkness, during the night-day cycle) [1,2]. In this way, melatonin production is controlled by an endogenous circadian timing system and is also suppressed by light. In lower vertebrates, the pineal gland is photosensitive (similar to a "self-sustaining circadian clock"); while, in humans the gland has been losing direct photosensitivity over time [3].

The pineal in mammals also shows circadian oscillations, which are damped as a function of time and by information from a primary circadian pacemaker [located in the suprachiasmatic nucleus (SQN), in the anterior portion of the hypothalamus] [4].

The duration of episodes of nocturnal melatonin secretion increases according to the length of the night, thus providing a kind of "internal calendar" that regulates seasonal cycles, reproduction and other functions (in photoperiodic species). Although humans are not considered photoperiodic, the identification of seasonal affective disorders and their successful treatment with light suggests that some capacity for photoperiodic response has been preserved [5,6].

In humans, exogenous melatonin has a soporific effect, but only when administered during the day or early at night (when endogenous levels are low). Some types of primary insomnia have been attributed to decreased melatonin production, especially in older people, but evidence for a causal link is still inconclusive [7].

Melatonin administration also has mild hypothermic and hypotensive effects. A possible role of this gland in reproductive processes has also been proposed, based on the effects of pineal tumors and melatonin levels on sexual development and the onset of puberty. Additionally, a probable effect of melatonin on the functioning of the immune system and its possible role as an antioxidant and oncostatic is also described, in addition to its association with some psychiatric and/or neurological disorders; finally, the pineal gland has been related to some spiritual aspects and mystical experiences [7-9].

HISTORICAL BACKGROUND

The first description of the pineal gland and the first speculations about its functions are found in the writings of the Greek physician and philosopher Claudius Galen Nicon of Pergamon (approximately 129-216 AD). Galen explained that the name of the gland was due to its similarity in shape and size to the nuts found in the cones of the stone pine [10].

He called it a "gland" because of its appearance and because he considered it had the same function as all the other glands in the body (supporting blood vessels). At the time, Galen assumed that the lateral ventricles of the brain were paired (which he called the "anterior ventricle"), he called the third ventricle "middle ventricle" and the fourth ventricle "posterior ventricle" [10,11].

Additionally, he thought that these ventricles were filled with *psychic pneuma* (a fine, volatile, airy or vaporous substance that he described as "the first instrument of the soul"). In this way, Galen attempted to refute the view that the pineal gland regulated the flow of *psychic pneuma* in the anatomical channel between the middle and posterior ventricles of the brain, since he was convinced that the gland was attached to the outside of the brain and because It had no movement of its own, in fact, it ensured that the epiphysis or apophysis of the cerebellum (today known as the superior vermis of the cerebellum) was much better qualified to perform that function [10,11-13].

Subsequently, several theories were proposed about the ventricular localization of the psychological faculties of the brain proposed by Galen. The first of them was proposed by Posidonius of Byzantium (at the end of the 4th century, AD), who considered that imagination was due to the anterior part of the brain, reason to the middle ventricle, and memory to the posterior part of the Brain [14].

Later, Nemesius of Emesa (5th century, AD) maintained that the anterior ventricle was the organ of imagination, the middle ventricle the organ of reason, and the posterior ventricle the organ of memory; this concept was almost universally accepted until the mid-16th century, with some modifications; for example, Avicenna (980-1037, AD), projected some psychological distinctions related to the "Soul" according to Aristotle, in the cerebral ventricular system [13-15].

Later, the Melkite physician and philosopher, Qusta ibn Luqa (864-923, AD) combined the doctrine of the ventricular location of Nemesius with the description of Galen, in the sense that he considered that there was a part in the brain similar to a "worm" that controlled the flow of spirit between the middle and posterior ventricle and proposed that people who wanted to remember looked up (because this action raised the worm-like particle and opened the path that allowed memories to be recovered from the ventricle later); while, people who wanted to think, looked down (because this lowered the particle, closing the path, protecting the spirit in the middle ventricle from being disturbed by the memories stored in the posterior ventricle) [16,17].

This conception of ancient thinkers contrasted with the concept that Rene Descartes later described in his book "The Treatise of Man"; for him, the pineal gland was involved in the phenomena of sensation, imagination and memory, and was the cause of bodily movements; however, some of Descartes' basic anatomical and physiological assumptions were completely wrong, not only by today's standards of knowledge, but also by the knowledge of the time; for example, Descartes thought that the pineal gland was suspended in the middle of the ventricles (something Galen had previously ruled out) and he also believed that the gland was filled with spirits, attracted by many small arteries surrounding it, and that these spirits were like "a very fine wind" or rather, a "very lively and pure flame" [18,19].

Additionally, he thought that these spirits inflated the ventricles – in the same way that the wind inflates the sails of a ship. Perhaps Descartes' most recognized concept was that the pineal "housed" the rational Soul of man (and he called it "The Third Eye") [17-19].

The most recent knowledge about the function of the pineal arises from the 1950s, where some properties were attributed to the gland regarding the control of gonadal function, skin color, its links with behavior and synthesis and melatonin secretion; subsequently, the term "neuroendocrine transducer" was coined to describe the pineal gland as an organ capable of converting the nervous signal from the retina into a chemical signal that produces melatonin [20,21].

While philosophy (in a reductionist vision) classified the pineal as just another part of the brain and science studied it as another gland, towards the end of the 19th century, Madame Blavatsky (founder of theosophy), identified and compared "The third eye" with the "eye of Shiva" of the Hindu mystics, and concluded that the pineal gland of modern man was an atrophied vestige of this organ of "spiritual vision" [22].

ANATOMY AND HISTOLOGY OF THE PINEAL GLAND

The pineal gland is also known as the epiphysis of the brain or the pineal body, it is an odd endocrine organ, located in the midline, it is an outgrowth of the roof of the diencephalon, with a conical shape and is oriented in an antero-posterior direction, resting over the groove that separates the superior colliculi with the posterior wall of the third ventricle, joining the habenular and posterior commissures by means of the pineal stalk [23].

The gland is bathed by cerebrospinal fluid and is covered by the pia mater, which forms a capsule from which septa project through which a large number of blood vessels enter, dividing it into lobules. The pineal has a weight between 100 to 200 mg and a length and width of 5-8 mm and 3-5 mm, respectively; furthermore, it is innervated by sympathetic fibers originating in the central nervous system [23,24].

For its part, the superior cervical ganglion of the paravertebral chain is the main post-ganglionic afferent (which gives shape to the pineal nerve). The first component of the innervation pathway is the retino-hypothalamic tract, which originates from retinal ganglion cells, located in the eye, and which are directed through the optic nerve and the chiasm until reaching the hypothalamus; the retino-hypothalamic tract projects into the ventrolateral suprachiasmatic nucleus, then to the hypothalamic paraventricular nucleus, and from this to the spinal cord, through the medial bundle of the forebrain [23,24].

The vascularization of the gland comes from the posterior cerebral arteries, from which the posterior choroidal arteries originate that surround the pineal capsule, penetrating it. The venous drainage converges into a thick vessel that, after joining the great cerebral vein, empties into the anterior portion of the straight sinus [24-25].

Embryonically, the pineal is a structure that derives from the caudal portion of the dorsal diencephalon, which will later form the epithalamus, and is formed by two main types of cells, the pinealocytes and the neuroglia cells, the pinealocytes (the main pineal cells) are highly modified neurons that are arranged in groups and cords, surrounded by a rich network of fenestrated capillaries and whose characteristic is a rounded granular nucleus, with a prominent nucleolus and a poorly stained cytoplasm (when stained with hematoxylin-eosin) [25,26].

With modern impregnation methods, pinealocytes appear with highly branched processes, some of them ending near or on blood vessels; cytoplasmic granules contain indolic compounds, such as melatonin and serotonin; for their part, the neuroglia cells (interstitial cells) are elongated and are dispersed among the pinealocytes (Figure 1).

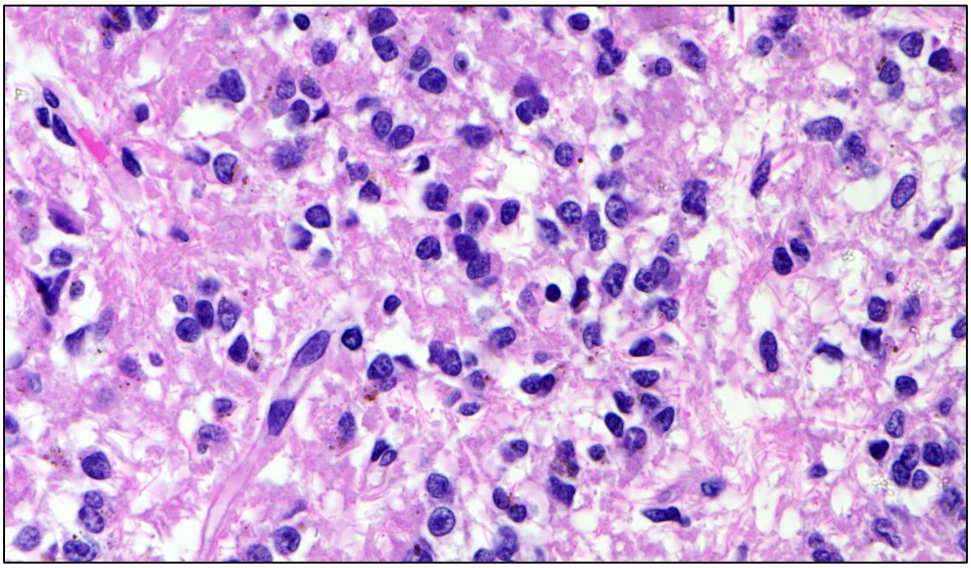

Figure 1. Normal pineal gland, composed of follicles and cords of pinealocytes that reside within the glial tissue. Pinealocytes have a poorly defined cytoplasm, with numerous appendages. The nucleus contains neuroendocrine vesicles rich in synaptophysin. Some calcifications or 'sandaceous bodies' can be seen. 40x section, hematoxylin-eosin stain.

Source: author's archive.

A characteristic detail in older people is the presence of extracellular basophilic bodies, called corpora arenacea or pineal grit, formed by concentric layers of calcium, carbon and magnesium phosphate, in the middle of an organic matrix, and which can, in resonance images, brain magnetic nuclear or computed axial tomography scan, look like a calcified gland [26,27] (Figure 2).

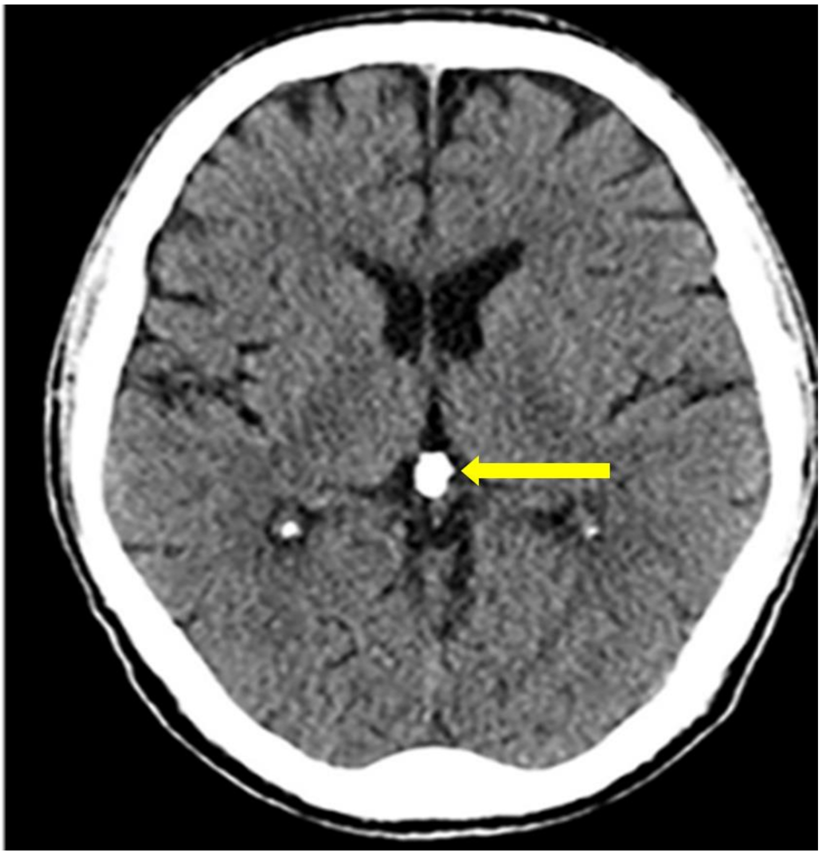

Figure 2. Computed axial tomography image of a calcified pineal gland (indicated by the yellow arrow) in a 68-year-old man.
Source: author's archive.

PINEAL PHYSIOLOGY AND MELATONIN SYNTHESIS

The main function of the pineal is to receive and transmit information from the environment about the light and dark cycle, through the cyclical production and secretion of melatonin during the night (dark period). Although in some species of lower vertebrates the pineal is photosensitive, this property is lost in higher vertebrates [28].

In the latter, retinal ganglion cells detect light and send neural signals to the visual areas of the brain. In addition, some retinal ganglion cells contain melanopsin and have intrinsic photoreceptor capacity, capable of sending neuronal signals to non-image-forming areas of the brain (including the pineal gland), through complex neuronal connections [29].

Photic information from the retina is sent to the SQN, which is the main system that generates the circadian rhythm or "clock", and from there, to other hypothalamic areas. When there is a light signal, the SQN secretes gamma-aminobutyric acid, responsible for the inhibition of neurons that synapse in the paraventricular nucleus (PVN) of the hypothalamus, interrupting the signal to the pineal, inhibiting the synthesis of melatonin. While, when there is no light signal (darkness), the SQN secretes glutamate, responsible for the transmission of the signal by the PVN to the pineal [28-30].

However, in the presence of darkness, the SQN can generate "rhythmic output" information (as it functions as an endogenous oscillator); therefore, the rhythm deviates beyond 24 hours (light-dark cycles serve to synchronize the rhythm to 24 hours). Melatonin (N-acetyl-5-methoxytryptamine) is synthesized within pinealocytes from tryptophan, and occurs mainly in the presence of darkness, when there is a significant increase in the activity of serotonin-N-acetyltransferase (arylalkylamine N-acetyltransferase, AA-NAT), responsible for the transformation of 5-hydroxytryptamine (5HT, serotonin) into N-acetylserotonin (NAS) [31,32].

NAS is converted to melatonin by acetylserotonin O-methyltransferase, both AA-NAT and the availability of serotonin play a role in limiting melatonin production. AA-NAT mRNA is expressed mainly in the pineal, retina and, to a lesser extent, in other areas of the brain, the pituitary gland and the testes. The activation of AA-NAT is triggered by the activation of β1 and α1b adrenoceptors by norepinephrine (NE), which is considered the main transmitter through β-1 adrenoceptors, potentiated by α-1 stimulation [32-34].

EFFECTS OF MELATONIN ON HEALTH OUTCOMES

Both the availability of NE and that of serotonin, stimulate the synthesis of melatonin and it has been found that sympathetic denervation (surgical or traumatic) of the pineal or the administration of β-adrenergic antagonists can suppress the rhythmic synthesis of melatonin and control over the "light-dark" stimulus [35].

It was recently found that, in the brain of rodents, melatonin is synthesized exclusively in the mitochondrial matrix, and then released into the cytoplasm, thus activating a mitochondrial MT1 signal transduction pathway (which is capable of inhibiting the release of cytochrome C, mediated by stress and the activation of caspases, thus intervening in the aspects of inflammation and cell death) [34-36].

Despite these findings, it is difficult to establish the definitive role of melatonin on possible health outcomes, since the different studies show considerable clinical and methodological heterogeneity – in terms of the populations evaluated (from newborns to the elderly), doses, excipients, quality or purity of melatonin preparations, control groups, measures of association, study designs, duration of follow-ups, clinical settings, etc.-

However, there is some support for the notion that melatonin (endogenous and exogenous) is associated with better health outcomes, such as cardiovascular disease, cancer, reproductive disorders, psychiatric disorders, autoimmune conditions (rheumatoid arthritis), asthma or in transplanted individuals, among others; these effects can be explained – at least in part – because melatonin is capable of stimulating the function of the immune system through the production of interleukins (IL-1, IL-2, IL-6 and IL-12), interferon-γ (IFN-γ), CD4 and CD8 T lymphocytes and T and B lymphocyte precursors [37].

It has also been suggested that some effects of melatonin are induced by anti-oxidant, anti-inflammatory, anti-apoptotic, anti-nociceptive, anti-hypertensive, cytoprotective, neuroprotective, cardioprotective or nephroprotective effects (since it is capable of improving the function mitochondria, protect nuclear and mitochondrial DNA and regulate homeostasis) [36-38].

Although some of the mechanisms of action are well established, the exact role of melatonin on various health outcomes is not very clear, due to the presence of multiple confounding factors, such as diet, exercise, sleep, genetic and epigenetic, which limits the ability to generalize the results of research in this regard [38].

Other functions of the pineal and melatonin seem to be related to pubertal development (the photoperiods linked to the secretion of melatonin determine the moment of onset of puberty, after reaching a certain degree of somatic maturation), the synchronization of reproduction, appetite, body weight and fat accumulation. It is also likely to synchronize general endocrine functions with environmental conditions most favorable for survival [39].

Other hormonal responses partially regulated by melatonin are the regulation of thyroid function (at the hypothalamic level or by direct effect on thyrocytes); it also seems to have an effect on the secretion of corticotropin and on the adrenal cortex (in the cells of the fasciculated layer), intervening in cortisol metabolism; additionally, in the adrenal medulla, pinealectomy or permanent light exposure eliminates the circadian rhythm of dopamine β-hydroxylase, inducing an inhibitory effect on catecholamine secretion. On the other hand, the stimulation of melatonin secretion (due to exposure to darkness) is associated with an increase in blood glucose levels and a decrease in plasma insulin concentration [40,41].

PATHOLOGY OF THE PINEAL GLAND

Abnormalities of the pineal gland arise primarily as cysts or tumors. Tumors can be divided into many subtypes, such as pineocytomas, pineoblastomas, papillary tumors of the pineal region, and parenchymal pineal tumors of intermediate differentiation. Pineal tumors currently represent between 0.4-1% of all intracranial tumors in adults and 3-8% in pediatric age (being more common in children between 1-12 years). In adults, these lesions are usually diagnosed in the third decade [42,43].

Tumors of the pineal region are more common in men in a 3:1 ratio and germ cell tumors are 12 times more common in men. All of these tumors are very rare and often develop before 20 years of age, with the exception of parenchymal tumors. The most frequent clinical manifestations are headache, vomiting and dizziness secondary to hydrocephalus, although visual alterations, diabetes insipidus and reproductive disorders (precocious puberty or delayed puberty) may also coexist [44].

Papilledema is a common ophthalmologic finding; in the presence of larger tumors or in which hemorrhage or infarction has been demonstrated (pineal stroke), several unique ophthalmologic abnormalities may occur, collectively known as Parinaud syndrome. These include upward gaze paralysis, convergence-retraction nystagmus, pupillary dissociation to light, retraction of the eyelids and eyes when exposed to the sun (which is a combination of upward gaze paralysis with eyelid retraction, resulting in preferential downward gaze that is combined with exposure of the sclerae) [45].

Parinaud syndrome is found in 50-75% of patients with pineal tumors. Additionally, there may be diplopia, which is caused by paralysis of the IV or VI cranial nerve (due to hydrocephalus or compression of the dorsal midbrain); occasionally, an increase in the vertical deviation of the eye is found when the head is tilted toward the side of the IV cranial nerve that is involved (called Bielschowsky's sign) [44-46].

When tumors are large, they can extend into the posterior fossa, compressing the superior vermis and superior cerebellar peduncles, producing ataxia and horizontal nystagmus. Compression of the midbrain tegmentum may result in weakness, apathy, ophthalmoparesis, mydriasis, anisocoria, and eyelid ptosis [45-47].

Precocious puberty of central origin is one of the comorbid disorders that can be observed with pineal gland dysfunction. Although clinical implications remain asymptomatic for years, precocious puberty is often observed in children or young adults. The role of melatonin in puberty is not very clearly defined; however, disorders of the hypothalamic-pituitary-gonadal axis are associated with a distorted plasma melatonin profile [47,48].

On the other hand, some psychiatric disorders (depression) have been associated with the secretory pattern of melatonin and the increase in the synthesis and release of corticotropin and cortisol; in fact, an increase in the clinical diagnosis of depression has been found associated with the decrease in the light period during the winter (where melatonin concentrations are very low), and although it is seen that when these individuals are exposed to light (of high intensity) the symptoms improve, no correlation has been found with the melatonin concentrations [48,49].

Likewise, patients diagnosed with bipolar disorder have greater sensitivity to the effects of light or melatonin suppression. Finally, it should be taken into account that a significant number of antidepressants potentially induce the secretion of melatonin (by increasing the availability of its precursors -serotonin and tryptophan-, norepinephrine) or by regulating the action of serotonin and catecholamine receptors [48-50].

GENERAL USES OF MELATONIN

Exogenous melatonin has been widely studied for its impact on sleep. A beneficial effect on sleep onset latency and other parameters in special populations (e.g., autism spectrum disorder, shift workers, jet lag, etc.) is well supported. In contrast, there is limited or equivocal data on the use of melatonin in outcomes such as atopic dermatitis, improved bone density, cardiovascular conditions, irritable bowel syndrome (predominantly constipation), periodontal disease, multiple sclerosis, balance, vertigo, among others. There are no data to support a role for melatonin in the treatment of cognitive impairment related to dementia and/or delirium, epilepsy, mood disorders, or organ transplant graft rejection. A weakness of all the studies is, for example, the therapeutic dose of melatonin that must achieve clinical benefit, the populations evaluated, the follow-up time, the way of measuring the outcome, the heterogeneity of the studies, the small sample size of the same, etc. [51-54].

Some outcomes evaluated in various types of studies are summarized in table 1.

Table 1. Some outcomes positively mediated by the use of exogenous melatonin. All results are based on low-quality studies, with high heterogeneity, with different doses and follow-up periods.

Health condition	Positive Melatonin Results
Pregnancy/breastfeeding	Melatonin Delayed Early Onset of Preeclampsia
Fibromyalgia	Melatonin (monotherapy) and in combination with amitriptyline, significantly decreased pain scores, compared to amitriptyline monotherapy, in addition to improving the function of the inhibitory pain modulation system
Generalized pain	Melatonin exerted a significant anti-nociceptive effect and decreased pain scores in patients with associated surgical pain under topical anesthesia, general anesthesia, inflammatory pain, pain during the procedure, and experimental pain
Headache/migraine	Melatonin improves the frequency of migraine attacks, the severity and disability associated with migraine, compared to the use of tricyclic antidepressants or placebo
Temporomandibular disorders	Melatonin improves pain and sleep quality, compared to placebo
Autism spectrum disorders	Melatonin improves sleep quality and efficiency
Glucose metabolism	Melatonin lowers fasting blood glucose levels and increases insulin sensitivity rates
Cardiovascular disease	Melatonin can lower blood pressure levels, reduces atherosclerotic plaque size, and oxidative stress
Circadian rhythm/ Jet lag	Melatonin improves sleep quality in the short term
Dermatological effects	Melatonin reduces IgE and IL-4 levels
Epilepsy	Melatonin significantly reduces the number of daytime seizures compared to placebo

Gastrointestinal Effects	Melatonin can have a positive effect on irritable bowel syndrome, constipation and constipation, by improving motility and sleep quality
Non-alcoholic fatty liver disease	Melatonin reduced the levels of PCR, AST, ALT and cytokines, compared to placebo
Infections	Melatonin reduces levels of inflammatory markers and improves white blood cell count in patients with sepsis
Insomnia and other sleep disorders	Melatonin improves sleep efficiency and quality
Reproductive System	Melatonin reduces pain scores in women with dysmenorrhea and pelvic pain from endometriosis

Source: author's elaboration.

THE PINEAL GLAND FROM A MYSTICAL-SPIRITUAL POINT OF VIEW

There is a large body of literature alluding to the pineal gland as a mystical-spiritual organ, indicating (according to popular belief) that the gland corresponds to the Sefira of Kether, The Crown, the Divine Unity that contains all things, or as the All-Seeing Eye, the Eye of Providence, the One Eye described in the Catholic Bible, and also the Eye of Horus and the Eye of the Cyclops [55].

For its part, Theosophy is defined as the direct knowledge of God; His search is Mysticism or Esotericism, common to all religions, put by Theosophy in a scientific form, as in Hinduism, Buddhism, Roman Catholicism and Sufism. Based on this, Theosophy proposes that the pineal gland is an atrophied vestige of an organ of "spiritual visión"; while, for the "energetic" or "spiritual" component of medicine, seven main energy centers are described at the body level (although for some, it could be eight, or even nine); in each of them it is assumed that they contain a spiritual teaching for life, these energy centers have been called "Chakras" [56,57] (figure 3).

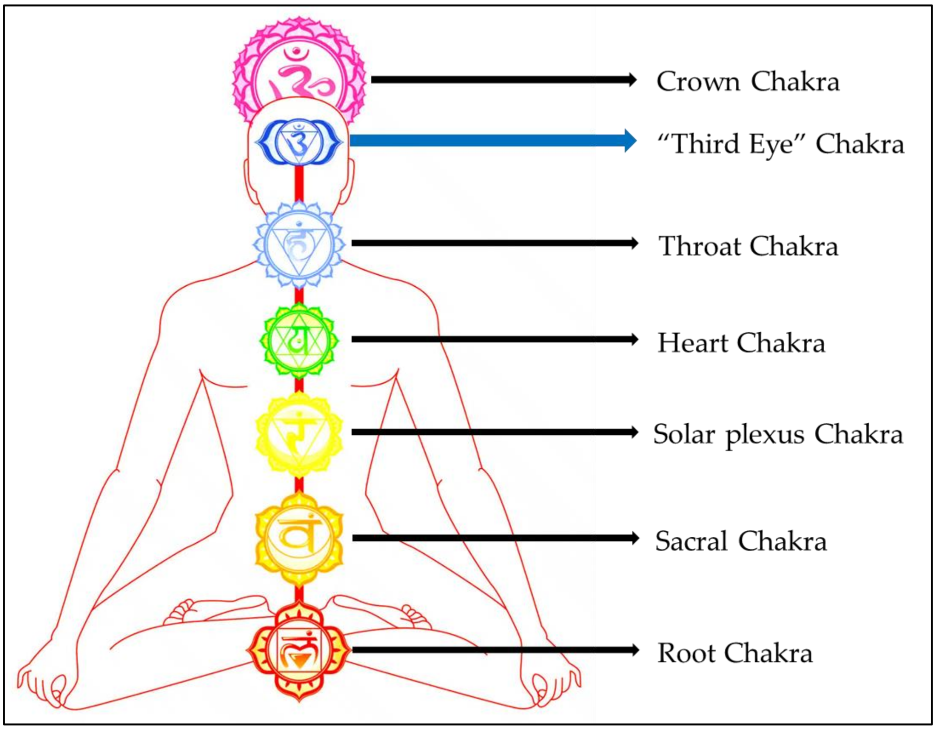

Figure 3. The term Chakra (or wheel, in Sanskrit) refers to the seven fundamental vortices of energy, located on the spine, from the tailbone to the cranial vertex. The Chakras define the points of physical and spiritual contact in humans, and are considered the bridges to reach higher levels of consciousness, representing the journey from the earthly plane to divinity.

Source: author's elaboration.

The Pineal Gland, A Bridge Between the Hormonal Perspective and Spiritual Mysticism

The knowledge of the Chakras is ancient and according to Hindu and Buddhist tradition, the seven Chakras constitute the traditional energy centers of the "astral" body (a subtle energy plane that coexists with the physical body), and are the areas of connection between the body and the Spirit. The sixth Chakra (or seventh, to some scholars) is known as the Third Eye Chakra or "Ajna", this energy center has been linked to intuition and the powers of precognition, as well as aspects of predicting the future, prophecy, channeling of wisdom from outside the Self, clarity and perspective of the past [58].

Therefore, it can be defined as an open channel of wisdom and understanding that challenges human understanding. The Third Eye Chakra corresponds anatomically to the pineal gland and it has been suggested that its dysfunction is associated with mental, emotional disorders and physical alterations, which are summarized in table 2.

Table 2. Mental, emotional components and health alterations related to the sixth or seventh Chakra ('Third Eye'), depending on its anatomical correspondence with the pineal gland.

Associated mental and/or emotional components	Related physical and/or mental illnesses
Self-esteem and values	Pineal and brain tumors
Emotional intelligence	Visual loss
Faith and inspiration	Hearing loss
Intuition and compassion	Learning disorders
Spirituality	Epilepsy
Devotion and mysticism	Dementia
Intellectual capacities	Cognitive impairment
Ethics and truth	Loss of creativity
Confidence	Depression
Humanitarianism	Anxiety
Generosity	Fibromyalgia
Learning from experiences	Chronic fatigue syndrome
Self-knowledge	Headaches
Connection with the Divine	Migraine
Prediction of the future	Vertigo
Wisdom	Extreme sensitivity to light and sound
Perspective of the past	Nonspecific polyneuropathies
Experience and vision of the present	Hydrocephalus
Receptivity of ideologies	Pubertal developmental disorders
Bravery	Insomnia

Source: author's elaboration.

Despite the ancient knowledge that has related the pineal gland to the Chakras or the "Third Eye", the evidence that demonstrates that the interventions of this energy center on health outcomes (based on observational or intervention studies) is very scarce. or non-existent, opening an interesting and novel field of research; until now, apart from the tumor pathology (of the pineal) and the interesting effects of melatonin on certain health conditions, this gland remains a great mystery, not only for endocrinology, but also in energy and spiritual medicine, however, for the other side (the wise mystics and great spiritual gurus) there is no doubt about the true role of the pineal gland in the human being, that is, the organ of energetic connection between the physical body, the emotional body. mental and Divinity [59,60].

CONCLUSIONS

Since ancient times, multiple descriptions of the pineal gland have been made, however, its functions in humans are not completely established. Its main secretion product (melatonin) has a "rhythmic" synthesis and release pattern specifically in the "dark" phase of the day-night cycle, controlled by a circadian synchronization phenomenon, which is suppressed by light. The pineal is also capable of responding to light, through multisynaptic pathways that involve retinal ganglion cells that contain melanopsin. For its part, the use of exogenous melatonin has a soporific effect, therefore, some types of primary insomnia have been attributed to a decrease in melatonin production. The administration of melatonin has also been associated with multiple other effects and outcomes, with inconclusive results. Finally, the pineal gland has been considered the "Third Eye" and is the gland that reflects the "bridge" between the physical world and the spiritual world.

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ABBREVIATION LIST

AA-NAT, Arylalkylamine N-acetyltransferase
5HT, 5-hydroxytryptamine, serotonin
IL, Interleukins
NAS, N-acetylserotonin
NE, norepinephrine
PVN, Paraventricular nucleus
SQN, Suprachiasmatic nucleus

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

CONFLICTING INTEREST

The authors declare that they have no conflicts of interest in the preparation of this article.

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