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Review

Fluoride and Pineal Gland

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Abstract: The pineal gland is an endocrine gland whose main function is the biosynthesis and secretion of melatonin, a hormone responsible for regulating circadian rhythms, e.g., the sleep/wake cycle. Due to its exceptionally high vascularization and its location outside the blood–brain barrier, the pineal gland may accumulate significant amounts of calcium and fluoride, making it the most fluoride-saturated organ of the human body. Both the calcification and accumulation of fluoride may result in melatonin deficiency.

Keywords: fluoride; pineal gland; calcification of soft tissues; melatonin

1. Introduction

The effect of fluoride on the human body is characterized by a very narrow margin of safety, which means that even relatively low concentrations may cause various adverse or even toxic effects [1–5]. The risk naturally increases with the intensity and duration of the exposure, with long-term exposure resulting in chronic poisoning [6,7]. One of the defense mechanisms protecting the body against the effects of fluoride toxicity seems to be its deposition in calcified tissues [2]. The most important role is played by hard tissues; bones; and teeth [2,8–10], in which fluoride accumulates in the form of fluorohydroxylapatite and fluoroapatite, replacing hydroxyl ions in the hydroxylapatite structure [11,12]. These processes may occur at any point in life, starting as early as in the prenatal period [13–15], and their effects are observed even in the skeletons and dentition of archaeological excavations from the times when exposure to fluorine compounds was incomparably lower to modern times [16–18]. Significantly, the deposition of fluoride in hard tissues may have its own adverse effects. The symptoms of excessive fluoride accumulation in bones and teeth are known and well documented, classified as skeletal fluorosis and dental fluorosis, respectively [19–24]. In addition to deposition in hard tissues, fluoride may also be found in calcification areas in soft tissues such as the aorta [25–29], coronary arteries [30,31], placenta [32–41], tendons [42–44], or cartilage [42,45,46]. In these cases, however, this accumulation may not be classified as a defense mechanism triggered by an excessive exposure to fluoride. Unlike in hard tissues, calcium accumulation in soft tissues is never a physiological phenomenon and almost always leads to some undesirable effects, e.g., complications in pregnancy [47,48]. This indicates that the saturation of soft tissues with fluoride is a natural consequence of their calcification. On the other hand, fluoride itself may stimulate the formation of calcification foci in the soft tissues [27,49], which suggests that fluoride accumulation is the primary phenomenon in calcification. Yet, regardless of the exact mechanisms, concentration of fluoride in the bloodstream, and thus the risk of adverse effects in the body, is reduced as fluoride accumulates in the soft tissues. Obviously, the exceptions to this are the fluoride-accumulating soft tissues; for example, extensive deposits of calcium fluoride in the placenta may impair blood flow through this organ and thus impair fetal nutrition [32,33,50,51].

One of the most interesting soft tissues able to accumulate fluoride is the pineal gland [1,52–55]. However, while knowledge of the calcification of this organ dates back to the 17th century [56], the first reports on its accumulation of fluoride appeared only in the mid-1990s [54].

2. Pineal Gland—Anatomy and Physiology

In humans, the pineal gland is a neuroendocrine gland weighing about 150 mg [57]. The organ, part of the epithalamus, is located between the *colliculi superiores* of the *lamina tecti*, at the back of the posterior wall of the third brain ventricle [58] (Figure 1). The pineal gland is characterized by a very rich network of blood vessels, which ensures blood flow of 4 mL/min/g, second only to the blood supply to the kidneys [58–60]. Another unique anatomical feature of the gland is its location outside the blood–brain barrier [58,59]. Therefore, unlike most other brain structures, the pineal gland has open access to blood and all of its components. Extremely rich vascularization and no significant restrictions in transport from the bloodstream make it possible for the pineal gland to accumulate significant amounts of various substances, mainly, calcium [58,61–66]; microelements such as cobalt, zinc, and selenium [67]; and fluoride [52–54].

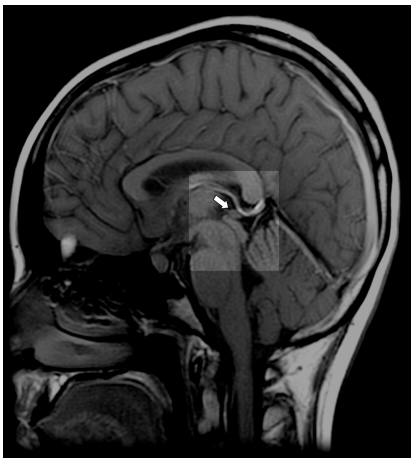

Figure 1. T1-weighted midline sagittal magnetic resonance imaging (MRI) with an arrow pointing to a normal pineal gland (case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 10767).

The basic function of the pineal gland is the production and secretion of melatonin [58,64], a hormone found in all vertebrates [60], including humans, which regulates circadian rhythms such as the sleep–wake cycle [64] (Figure 2). It is also a strong antioxidant [68–70] and an anti-inflammatory agent [71,72]. Although melatonin can be synthesized in almost all organs and tissues, including skin [73], intestines [74], bone marrow [75], testicles [76], ovaries [77], or the placenta [78], the proper biological response is regulated by the pineal hormone [64].

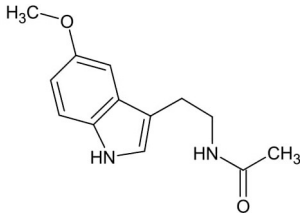

Figure 2. Chemical structure of melatonin.

Biosynthesis of melatonin (Figure 3) occurs in pinealocytes, which constitute about 95% of the pineal gland's volume [79]. The remaining part of the organ consists of astrocytes, microglia, vascular endothelial cells, and nerve fibers [79,80]. The precursor of melatonin is

tryptophan [58], and most of the hormone is produced during sleep [81]. Its plasma concentration reaches its maximum between 2 and 3 o'clock in the morning (80–150 pg/mL) [82]. The mechanism conditioning this effect is initiated by reducing the activity of the suprachiasmatic nuclei, which occurs at night. The effect is the activation of postganglionic sympathetic fibers and the release of norepinephrine from their nerve endings. This neurotransmitter stimulates β-adrenergic receptors, inducing activation of the adenylate cyclase-cyclic adenosine monophosphate (AMP) system. As a result of the increased cyclic adenosine monophosphate (cAMP) concentration in pinealocyte cytosol, the activity of serotonin N-acetyltransferase increases, which leads to the stimulation of melatonin synthesis [83,84].

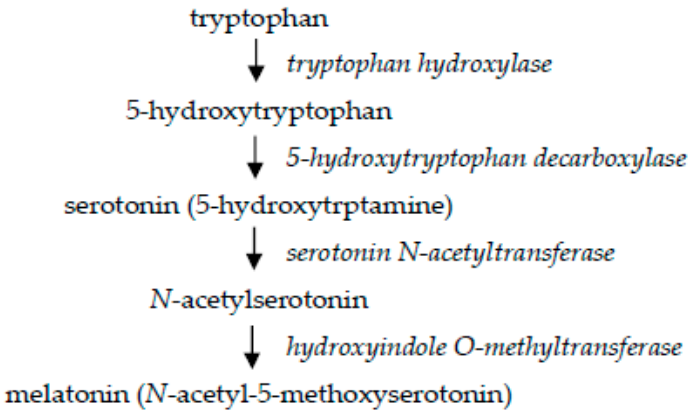

Figure 3. Biosynthesis of melatonin.

3. Calcium Accumulation in the Pineal Gland

Calcium accumulates in the pineal gland in the apatite structure, similar to that found in bones and teeth [63,85,86], and as calcium carbonate (calcite) [87]. The process is initiated in childhood [88], and even in newborns [89,90], so some scientists see it as a physiological phenomenon [64]. It is, however, difficult to agree with such a conviction in the face of ample evidence showing the relationship between pineal calcification and various pathological states. This includes mental illnesses and disorders [91–93], neurodegenerative disorders [94,95], primary brain tumors [96], ischemic stroke [97], migraine [98], and sleep disorders [99]. The accumulation of calcium in the pineal gland is also related to aging processes [100] (Figure 4).

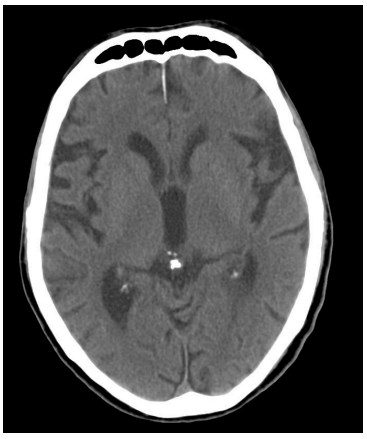

Figure 4. Computer tomography (CT) scan through the brain with calcification of the pineal gland (case courtesy of Radswiki, Radiopaedia.org, rID: 11770).

In the study in adolescents and adults, Kunz et al. [61] demonstrated an inverse correlation between the degree of pinealocyte calcification and pinealocyte count. Although there was no significant

correlation between gland calcification and plasma melatonin concentration, it was noted that the reduction in pinealocyte count caused by calcification was accompanied by a reduction in melatonin synthesis. Hence, the conclusion that pineal gland calcification has an indirect effect on the production and secretion of this hormone. These observations were confirmed by Liebrich et al. [101], who, using magnetic resonance imaging, showed a positive correlation between the size of the uncalcified part of the pineal gland and the concentration of melatonin in saliva.

According to some authors, the concentration of melatonin in the cerebrospinal fluid plays a decisive role in the regulation of circadian rhythms, while plasma hormone concentrations are of little importance in exerting biological effects in this respect [102,103]. As pineal calcification results in the reduction of melatonin concentration in the cerebrospinal fluid, its relation to diseases of the central nervous system becomes understandable. The pathomechanism of this relationship is to reduce the antioxidant effects of melatonin, which favors neuronal damage by reactive oxygen species (ROS) and, thus, to accelerate the development of neurodegenerative changes [64,70]. For example, it has been found that the concentration of melatonin in the cerebrospinal fluid in Alzheimer's disease is only 20% of that recorded in healthy individuals [104].

4. Fluoride Accumulation in the Pineal Gland and Its Consequences

Both calcified and calcium-free areas of the pineal gland undergo mineralization and accumulate, among other things, magnesium, iron, manganese, zinc, strontium, or copper [105]. However, it was not until the 1990s that it was discovered that the foci of calcification within the gland may be accompanied by extremely high concentrations of fluoride for soft tissue [54]. In 2001, Luke [52] first published the results of fluoride concentration measurements in pineal glands taken from human corpses. The mean concentration was 297 mg F/kg of wet weight (ww), but the range of recorded values was very wide (14 mg/kg–875 mg/kg ww). It is not difficult to notice that they are similar or even higher than those observed in bones and teeth and many times exceed the concentrations observed in other soft tissues (e.g., in muscles, they are about 1 mg F/kg ww). After converting these values into dry weight (dw), we obtain concentrations of 1485 + 1285 mg F/kg dw. Although these data come from older individuals (studies were conducted on a group of deceased people aged 70 to 100 years), this does not disprove the idea that the pineal gland may be considered the most fluoride-saturated organ of the human body. It has been observed that the fluoride content in pineal gland apatite is higher than in any other natural apatite and may even reach 21000 mg/kg [52,53].

The results of Luke's research also revealed a strong positive correlation between calcium and fluoride concentrations ($r = 0.73$, $p < 0.02$) [52]. Ten or so years later this observation was confirmed, albeit not for the full range of fluoride concentrations. Tharnpanich et al. [53] demonstrated that a statistically significant correlation occurs only when the fluoride concentration exceeds 50 mg/kg of fresh gland tissue. They recorded the values of these concentrations, which ranged anywhere from 0 mg F/kg ww to 831 mg F/kg ww (mean 75.5 + 228 mg F/kg ww). This suggests that the accumulation of fluoride in the pineal gland is rather a secondary phenomenon to the primary calcification of this organ and at some point the relation between them reaches the status of a very strong positive correlation ($r = 0.915$, $p < 0.001$). It is also worth noting that pineal glands in the study by Tharnpanich et al. [53] were collected from deceased persons aged 33 to 91 years (mean 67 years), who had inhabited an area with low fluoride contamination, which is a strong argument for the idea that a smaller or larger accumulation of fluoride in the gland occurs even when the organism is not exposed to particularly large amounts of fluorine compounds in the environment.

Regardless of how accumulation of fluoride in the pineal gland takes place, whether this is primary or secondary to calcification, the most important issue is the effects of this phenomenon. It is obvious that they will primarily concern the physiological function of the gland.

Assuming the preferential accumulation of fluoride in the pineal gland and the related possible risk of toxic effects, Malin et al. [11] have recently published a study on the processes of sleep regulation among older adults in the United States. They tried to answer the question of whether chronic exposure

to low doses of fluoride has an effect on sleep patterns and daytime sleepiness in the studied population. The study investigated adolescents aged 16–19 years (mean = 17 years), who had declared that they had no sleeping disorders, who were exposed to low doses of fluoride (mean concentration in drinking water = 0.39 mg/L), and who had low concentrations of fluoride in plasma (mean = 0.35 μmol/L). Higher water fluoride levels were connected with higher odds of participants reporting snorting, gasping, or apnea, while sleeping at night. Additionally, adolescents who lived in areas with higher fluoride levels in tap water experienced more frequent daytime sleepiness. The authors [11] were of the opinion that fluoride exposure may contribute to increased pineal gland calcification and subsequent decreases in nighttime melatonin production that contribute to sleep disturbances.

For obvious reasons, there are very few reports on the accumulation of fluoride in the pineal gland and its effect on the functionality of the organ in humans. Therefore, it is worth noting the studies carried out in both experimental and free-living animals.

In the pineal glands taken from the common merganser (*Mergus merganser*), Kalisińska et al. [1] recorded very high fluoride contents (mean > 1000 mg/kg dw), which even exceed the concentrations observed in the bones of these birds. Such a high concentration of fluoride in the gland is explained by the incompleteness of the blood–brain barrier in birds, which facilitates the penetration of various substances into the central nervous system.

Mrvelj and Womble [79] conducted a study to determine the effect of fluoride removal from the diet of aged rats (over 26 months of age) on the pineal cell structure and to compare the results with rats receiving fluoride with food (control). It was observed that in animals deprived of fluoride for 8 weeks, the number of pinealocytes was higher than in control animals, which suggests a harmful effect of fluoride contained in the diet on pineal morphology and thus on the production and secretion of melatonin.

In turn, studies conducted by Bharti and Srivastava [106,107] in rats showed the beneficial effect of melatonin and pineal proteins on fluoride-induced oxidative stress, which is one of the best known effects of fluoride on the body [108,109]. The animals were exposed to different doses of fluoride and melatonin and proteins obtained from buffalo pineal (*Bubalus bubalis*). The severity of oxidative stress was measured by the degree of activity of antioxidative enzymes: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), as well as the concentration of reduced glutathione (GSH) and malondialdehyde (MDA) in the brains of the animals [6]. The antioxidant system parameters were markedly improved by the intake of melatonin and pineal proteins; in the latter case, the beneficial effect was even stronger. The action consisted of increased activity of antioxidant enzymes, increased GSH concentration, and decreased MDA concentration. All these parameters were adversely affected in the group of animals receiving fluoride only (decreased activity of enzymes and GSH concentration and increased MDA concentration, which is a marker of increased oxidative stress), painting a very disturbing picture of the effects of fluoride accumulation in the pineal gland. Since it is known that fluoride reduces the production and secretion of melatonin [79], a substance which reduces the oxidative stress induced by them [107], the accumulation of fluoride in the pineal gland may be a significant factor in enhancing the effects of reactive oxygen species, with all potential adverse consequences.

Finally, it is worth mentioning that the concentrations of fluoride in the pineal gland at the magnitude of several dozen or even several hundred mg/kg ww, revealed in the studies by Luke [52] and Tharnpanich et al. [53], may show inhibitory activity on melatonin synthesis pathway enzymes. Fluoride having this effect has been known for a long time in relation to many enzymes [108,110]. Thus, it cannot be excluded that the restriction of melatonin synthesis associated with pinealocyte calcification may be caused not only by a decrease in the number of active pinealocytes but also by the direct influence of fluoride accumulated in the gland on enzymatic activity. This issue undoubtedly needs to be clarified in the future.

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