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Fluoride's Neuroendocrine Impact: A Comprehensive Review of Pineal Gland Dynamics

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Abstract

The pineal gland also called as pineal body or epiphysis cerebri is a tiny endocrine gland in the middle of the brain located beneath the back part of the corpus callosum that helps to regulate the body's circadian rhythm of sleep and wakefulness by secreting the hormone melatonin. Fluoride is a naturally occurring mineral present in the environment and its concentration varies from region to region. Humans and animals are exposed to fluoride mainly by food, water and air. It is present in the highest concentration in bones and teeth. Fluoride varnish is a natural material that is collected from trees and composed of resins that are rich in fluoride. They are widely used in dentistry as a preventive measure. The pineal gland is located outside the blood-brain barrier and has open access to blood and all of its components including fluoride. Excessive exposure to fluorine can also have harmful effects such as permanent damage to all brain structures, impaired learning ability, memory dysfunction and behavioural problems. And pineal gland calcification has an indirect effect on the production and secretion of melatonin hormone. As there is an increase in pineal gland calcification there are subsequent decreases in night time melatonin production that contribute to sleep disturbances in the people. So, the study aims to provide an overview related to the influence of fluoride accumulation on the physiological functions of the pineal gland and indirectly on the body's function and activity.

Keywords: pineal gland, fluoride varnish, calcification, sleep, melatonin

Introduction

Endocrine glands release hormones directly into the bloodstream. Hormones are chemicals that carry signals to different parts of the body. The pineal gland also

called the pineal body or epiphysis cerebri is a tiny endocrine gland in the middle of the brain located beneath the back part of the corpus callosum that helps to regulate the body's circadian rhythm of sleep and wakefulness by secreting the hormone melatonin1. It has a very rich network of blood vessels, which have a blood flow of 4ml/min/g. It is the second richest blood capillary network after the kidney network[2]. The main function of the pineal gland is to get information about the daily day-night cycle from the retinas of the eyes and then produce and secrete melatonin accordingly that is its level increases at night (during dark hours) and decreases in the day (during light hours). Melatonin is a hormone that helps to synchronize circadian rhythms in different parts of the body. Circadian cycles are physical, mental and behavioural changes that follow a 24-hour cycle. It also helps in the maintenance of normal sleep patterns.

Fluoride is a naturally occurring mineral present in the environment and its concentration varies from region to region. Humans and animals are exposed to fluoride mainly by food, water and air. It is present in the highest concentration in bones and teeth. It is accumulated in bone and its concentration increases with age[3.] Replacement of the hydroxyl (OH-) group in hydroxyapatite [Ca5(PO4)3(OH)] by fluoride ion(F-) forms fluorapatite which is more crystallised structures and a compound which strengthens the teeth against attack by organic acids produced by the fermentation of organic substances in the mouth6.Fluoride varnish is widely used in dentistry as a preventive measure because it acts as one of the several sources of additional fluoride administration and was developed to prolong the time of contact between the tooth surface and the fluoride thus reinforcing the tooth structure and making it less susceptible to carious lesions[38]. Fluoride deposition in the pineal gland hydroxyapatite is present in more concentrations than in any other part of the body, including bones and teeth5. In 2006, a National Research Council report concluded that fluoride is likely to affect pineal gland function and cause decreased melatonin production which could contribute to a variety of effects in humans4. Fluoride accumulation results in the reduction of melatonin concentration in the cerebrospinal fluid and thus causes diseases of the central nervous system. The pathomechanism behind this is due to the reduction in antioxidant effects of melatonin, which causes neuronal damage by reactive oxygen species (ROS) and, thus accelerates the development of neurodegenerative changes[7]

Methodology

To review the literature, studies were selected from PubMed, Scopus, Web of Science, and Google Scholar without restrictions on publication year, to provide a comprehensive overview of current knowledge regarding the impact of fluoride on the physiology and function of the Pineal gland. The review focused on evaluating the accumulation of fluoride in the Pineal gland and how it affects the different neuroendocrine functions. The search terms included: "Pineal Gland," "Fluoride," "Calcification," "Sleep cycle," "Melatonin," "Central Nervous System," "Blood-Brain Barrier," "Circadian Rhythm," and "Fluoride Varnish". The research encompassed, Case reports, laboratory studies, clinical studies, and systematic reviews.

Pineal gland anatomy, physiology and its functions

Pineal gland is a part of the epithalamus, and is located between the colliculi superioris of the lamina tecti, at the back of the posterior wall of the third brain ventricle[8]. Alongwith a rich vascular supply, one more unique anatomical feature of the gland is that it is located outside the blood-brain barrier and has open access to

blood and all of its components[9].So very rich vascularization and no significant restrictions from the bloodstream cause accumulation of significant amounts of various substances, mainly, calcium microelements such as cobalt, zinc, and fluoride[10]. The basic function of the pineal gland is the production and secretion of the hormone melatonin which is present in all vertebrates including humans, and regulates circadian rhythms that are sleep-wake cycle[7]. It is also a strong antioxidant and an anti-inflammatory action[12]. Melatonin acts as negative feedback to the biological clock, the suprachiasmatic nucleus (SCN) that regulates the circadian rhythm of the body SCN then sends signals to all the organs of the body to synchronize the day-night cycle which helps them to function in the proper time[13.]

Another function of the Pineal gland is that it might affect bone metabolism because some research on mice suggested that a change in the function of the gland may affect bone. Also, melatonin secreted by the pineal gland helps to maintain the sleep cycle but in older age, the gland secrete less melatonin and this may cause age related problems older adults sleep less with have trouble falling asleep so changes in melatonin might explain this phenomenon. Sleep deprivation can cause some mental disorders.

Fluoride role in the body

The amount of fluoride present in plants and animal food depends on its concentration in soil, water used for irrigation and air deposition. Human daily fluoride intake from food is low. There is a low concentration of fluoride in vegetables, fruits, pulses and also in meat, poultry and fish because most of the fluoride is accumulated in bones and teeth. So, most of the fluoride is derived from fluoridated water. Of the received fluorine, 75 %–90 % undergoes absorption in the stomach and intestines, and 99 % of the fluorine is transported to tissues rich in calcium (mainly to hard tissues) through the circulatory system[14].It helps in the mineralisation of bone in the body. It also helps in the formation of dental enamel and the development of teeth, preventing dental caries. Fluoride and calcium have a strong affinity toward each other and hence work together for the maintenance of bone.

Effect of fluoride on CNS

Prolonged exposure to fluorine in the prenatal and postnatal stages of development causes a toxic influence on the metabolismand physiology of neurons and glia which results in disorders related to memory and learning. In the neonatal period also, it is dangerous because it can penetrate through the placenta and can cross the blood-brain barrier[13]. Fluorine causes neurodegeneration due to oxidative stress, glial activation and inflammation in the CNS. Excessive exposure to fluorine can also have harmful effects such as permanent damage of all brain structures, impaired learning ability, memory dysfunction and behavioural problems.[15] But exact mechanisms by which fluorine decreases cognitive, and learning abilities and causes memory loss are not clear hence more studies are required to explore this concept. Defensive mechanisms of young individuals are less resistant to the toxic influence of fluorine because they are not fully developed and the permeability of their blood-brain barrier is higher than adults. A latest experimental study where the rat hippocampal neurons were incubated with various concentrations (20 mg/L, 40 mg/L, and 80 mg/L) of sodium fluoride in vitro concluded that fluoride neurotoxicity may target hippocampal neurons[16.] Many epidemiological studies carried out in geographical areas where fluorine content in drinking water is high showed that children who live in those areas have a statistically significant decreased level of intelligence in comparison

to the other children from regions where drinking water is not contaminated with fluorine[14]. During development central nervous system has weakened protective mechanisms and hence it is highly sensitive to the influence of fluorine.

Research by Luke in 2001 showed that in the human pineal gland, Fluoride ion reaches a very high concentration that is greater than in the bones, which is probably related to the presence of fluorapatite-containing concretions in the gland[5]. It has also been shown experimentally that Fluoride ions are neurotoxic and adversely affect the functioning of the brain, even at small doses. It contributes to the induction of apoptosis of neurons, formation of oxidative stress, increased amounts of free radicals and lipid peroxidation in the brain and inhibits the production of antioxidant enzymes, mitochondrial enzymes of energy and glutamate transporters[17]. So, this causes decreased activity in the mouse or rat brain and impaired memory or learning ability in animals and humans. Studies suggest that there are effects of fluoride exposure on children's neurodevelopment but in future, this should formally evaluate dose-responserelationship including mostly prenatal exposure assessment and their neurobehavioral performance, in addition to improving assessment and control.

Calcification of pineal gland

Ostrowski et al. 1980 concluded that in humans, at least some calciferous concretions are present in the soft tissues that are composed of hydroxyapatite and fluorapatite[19]. Among the soft tissues, calcium and fluorine compounds in the form of calcifications are mainly found in mammal brains. The human pineal has been called the fifth mineralizing tissue since it is one of the rare tissues in the body where physiological calcification occurs. It is considered to be a 'normal' phenomenon because it is not usually associated with any clinical symptoms[10].In various parts of the brain, calcified concretions are formed naturally with the intrapineal calcifications which are described, mainly in mammals and also in bird18. Hence increased calcification of the pineal gland will cause a decrease in the number of functions of the pineal gland due to a decrease in pinealocytes which are cells of the pineal gland which results in a decreased ability of the gland to produce melatonin. Further, it is confirmed that calcification of pinealocytes results in death or degeneration of the cell itself, thus leading to an overall decrease in pineal activity[20]. Hence, to conclude that pineal gland calcification has an indirect effect on the production and secretion of melatonin hormone. This conclusion was confirmed by Liebrich et al. in the study using magnetic resonance imaging that showed a positive correlation between the size of the uncalcified part of the pineal gland and the concentration of melatonin in saliva[11]. Some studies show that the concentration of melatonin in the cerebrospinal fluid plays an important role in the regulation of circadian rhythms. Pineal calcification results in the reduction of melatonin concentration in the cerebrospinal fluid which results in diseases of the central nervous system. The Patho mechanism behind this is to reduce the antioxidant effects of melatonin, which favours neuronal damage by reactive oxygen species (ROS) and it will accelerate the development of neurodegenerative changes.[7]

Pineal gland calcification is mainly composed of hydroxyapatite (HA) which is very similar to that found in bones or teeth. Factors that are considered as related to increased pineal calcification are increasing age, male gender, high altitude, and increased intensity of sunlight exposure[21]. Thus, thestrong correlation between the pineal calcium and fluoride contents in the study implies

that pineal fluoride incorporation is related to calcification[1]

Fluoride accumulation in the pineal gland

One of the unique features of the pineal gland is that it is situated outside blood blood-brain barrier and is one of the regions in the brain (all midline structures bordering the third and fourth ventricles) where the blood-brain barrier is weak. So, cells in this region are in direct contact with blood that is pinealocytes are also directly related to blood and its product and thus free to absorb fluoride from the bloodstream[22]. If there had been a blood-brain barrier in the pineal gland then it would have prevented the uptake of fluoride by pinealocytes. And high fluoride level is also due to profuse blood flow and high capillary network as the pineal gland has the second richest capillary network after the kidney[2]. It was observed in many studies that when animals are deprived of fluoride for 8 weeks, the number of pinealocytes was higher than in control animals, which suggests that fluoride affects pineal gland melatonin production and secretion[24]. Fluoride deposition in pineal gland hydroxyapatite is present in higher concentrations than in any other part of the body, including bones and teeth[5.]

Fluoride has inhibitory activity on enzymes of the melatonin synthesis pathway. So, inhibition of melatonin synthesis is not only associated with pinealocyte calcification and a decrease in the number of active pinealocytes but also due to the direct influence of fluoride accumulated in the gland on enzymatic activity[33]. But this issue must be clarified with the help of more studies. Many studies show great differences in brain fluoride concentrations between birds and mammals to a lesser extent in the pineal gland. This may be due to food preferences, population areas and the amount of fluoride present in the environment. All these have their different biology and anatomy that is the different structures of the brain and blood-brain barrier. One of the experimental studies on rodents states that fluoride ions may alter the metabolism of glucose by decreasing the capacity to synthesize glucose and cause glycogen accumulation in the brain and other tissues[32].

Consequences of fluoride accumulation in the pineal gland

Some studies show that higher water fluoride levels cause snorting, gasping, or apneawhile sleeping at night in people. Additionally, persons who lived in areas with higher fluoride levels in tap water experienced more frequent daytime sleepiness. So, this may conclude that fluoride exposure may contribute to increased pineal gland calcification and subsequent decreases in nighttime melatonin production that contribute to sleep disturbances in people[23]. Fluoride also reduces the production and secretion of melatonin which helps to reduce the induced oxidative stress by them[25]. Research by Luke also suggested that in the human pineal gland, Fluoride reaches very high concentrations, greater than in the bones, which is probably due to the presence of fluorapatite-containing concretions in the gland[5]. Fluoride also highly influences the central nervous system during childhood development and causes problems like impaired ability to learn, disturbances in memory and information processing and behavioural problems.

It is found that each 0.52 mg/L increase in household tap water fluoride concentration was associated with a 1.97 times higher likelihood of adults reporting symptoms of having sleep apnea at least once per week[26]. A greater degree of pineal calcification among older adults is associated with decreased melatonin production and this will lower REM sleep percentage, greater sleep disturbances and daytime tiredness, decreased total sleep

time, and poorer sleep efficiency[27]. Interestingly, there is emerging evidence from many studies that melatonin may be effective in the treatment of adult and pediatric sleep disturbances like central and obstructive sleep apnea, which conclude that low melatonin production may play an etiological role in these disorders[28].But more animal and human studies are needed to explore this hypothesis.

There is also another fact that higher water fluoride concentrations are associated with an increased incidence of hypothyroidism and diabetes among adults which are associated with an increased risk of obstructive sleep apnea in these patients[29]. Additionally, prenatal and childhood fluoride exposure is also associated with an increased prevalence of Attention-deficit/hyperactivity disorder (ADHD)30 and this disorder is also associated with poorer sleep quality[31].

Effect of Fluoride Varnish

Fluoride varnish is a natural material that is collected from tree and composed of its resins that are rich in fluoride. They are widely used in dentistry as a preventive measure. The active ingredient in fluoridevarnishes is most commonly a 2.26% fluoride from a suspension of 5% sodium fluoride (NaF)[35]. Duraphat was the first commercially available product that contained fluoride varnish[34]. Recent studies confirmed that the fluoride varnishes become more superior when enriched with calcium compounds, such as casein phosphopeptide amorphous calcium phosphate (CPP-ACP) and phosphate tri-calcium (TCP)[36]. This CPP-ACP acts as a neutralizer to the acid produced in the oral cavity thus increasing pH values decreasing demineralisation and enhancing the remineralization of incipient carious lesions by hydrolyzing hydroxyapatites and also help in inhibiting the growth of bacteria in oral cavity[37]. It contains a large concentration of fluoride 22.6 mg/ml contains 22,600 ppm of fluoride ion. And when we apply fluoride varnish to patients, they are instructed not to brush their teeth for 24 hours so the varnish that we have applied to the tooth surface is mostly ingested and not expectorated by the patient. So continuous fluoride is secreted in saliva and salivary levels increase as plasma levels increase. Most of Fluoride enters the body via the gastrointestinal tract and it is quickly absorbed in the stomach without any specialized enzymatic systems. As soon as it is absorbed, plasma fluoride levels increase in 10 minutes reach at peak levels in 60 minutes and take 11 to 15 hours to return to basal level[42].

Ekstrand et al., when evaluating the plasma fluoride concentration and urinary fluoride excretion after application of Duraphat varnish his study revealed that urinary fluoride concentration after 12 hrs of application of Duraphat was between 500-1,100 μg F ion[40]. As the potentially toxic dose for fluoride is 5 mg/kg, the probable toxic dose for a child weighing 20 kg is approximately 100 mg[35]. So as the absorption of Fluoride varnish is much less than the toxic dose it might not affect the pineal gland. Toxicity of fluoride is mainly due to burning the tissues because of forms hydrofluoric acid when it comes in contact with them, impeding nerve function as it have affinity for calcium required for nerve function, cellular poisoning because inhibition of enzyme like melatonin and other and impeding cardiac function due to an electrolyte imbalance[39,41]. Studies are still going on fluoride varnish till then their application must be carefully monitored until further data proves its effect.

Conclusion

So, to conclude regardless of how fluoride accumulates in the pineal gland and whether this is primary or secondary to calcification, the mostimportant issue is the

effects of this phenomenon on the physiological functions of the pineal gland and indirectly on the body function and activity. In the future increasing degree of pineal calcification might be established as an indicator of the intra-individual decrease of the pineal gland's melatonin production which again influences the circadian rhythm or sleep-wake cycle of the individual.

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