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REVIEW ARTICLE

Effects of the f uoride on the central nervous system

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KEYWORDS
Fluoride;
Health;
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Abstract
Introduction: Fluorine (F) is a toxic reactive element and exposure to it passes almost unnoticed with the consumption of tea, f sh, meat, fruits, etc. and articles in common use such as: toothpaste additives; dental gels, non-stick pans and razor blades as Tef on. It has also been used with the intention of reducing dental caries.
Development: Fluoride can accumulate in the body and it has been shown that continuous exposure to it causes damaging effects on body tissues, particularly the nervous system directly without any previous physical malformations.
Background: Several clinical and experimental studies have reported that F induces changes in cerebral morphology and biochemistry that affect the neurological development of individuals as well as cognitive processes, such as learning and memory.
F can be toxic by ingesting one part per million (ppm), and the effects are not immediate, as they can take 20 years or more to become evident.
Conclusion: The prolonged ingestion of F may cause signi f cant damage to health and particularly to the nervous system. Therefore, it is important to be aware of this serious problem and avoid the use of toothpaste and items that contain F, particularly in children as they are more susceptible to the toxic effects of F.
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PALABRAS CLAVE
Flúor;
Salud;
Sistema nervioso

Efectos del f úor sobre el sistema nervioso central

Resumen
Introducción: El f úor (F) es un elemento tóxico y reactivo; la exposición al mismo pasa casi inadvertida con el consumo de té, pescado de mar, carnes, frutas, etc., y el uso de artículos como aditivo en pastas de dientes, enjuagues bucales, antiadherentes sobre sartenes y hojas de afeitar como el te f ón. Asimismo, ha sido utilizado con la intención de reducir la caries dental.
Desarrollo: El F puede acumularse en el organismo y se ha demostrado que la exposición crónica al mismo produce efectos nocivos sobre distintos tejidos del organismo y de manera particular sobre el sistema nervioso, sin producir malformaciones físicas previas.
Fuentes: Diversos trabajos, tanto clínicos como experimentales, han reportado que el F provoca alteraciones sobre la morfología y bioquímica cerebral, que afectan el desarrollo neurológico de los individuos y, por ende, de funciones relacionadas con procesos cognoscitivos, tales como el aprendizaje y la memoria.

La toxicidad del F se puede presentar a partir de la ingesta de 1 parte por millón (ppm) y los efectos no son inmediatos ya que pueden tardar 20 años o más en manifestarse.
Conclusión: La ingesta prolongada de F provoca daños a la salud y de manera importante sobre el sistema nervioso central, por lo que es importante considerar y evitar el uso de artículos que contengan f úor y de manera particular en individuos en desarrollo, debido a la susceptibilidad que presentan a los efectos tóxicos del F.
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Introduction

Fluorine (F) is a toxic, reactive element; exposure to F in human beings goes practically unnoticed thanks to the use of f uoride-containing compounds as additives in toothpaste (1,000 to 1,500 ppm), mouthwash (230-900 ppm of f uoride), in dietary supplements, and surface polymers found as non-stick surfaces in frying pans and razor blades, and the use of compounds with f uoride in the form of: industrial compounds, fertilizers, glass, oil re f neries, f uorinated fuels, and others.[1] Thus, a signif cant proportion of F in the body comes from being exposed to it and from eating certain food with a naturally occurring high content in F, such as tea, sea f sh, meats, eggs, fruits, and cereals. However, regular drinking water is the leading source of intake of this element.[1]

The water containing the highest concentration of f uorides corresponds to water resources located in mountainous regions or areas with geological deposits of marine origin, such as in Southeast Asia and Northeast Africa.[1] Studies conducted in the last 15 years show that a signif cant number of people in towns exposed to f uoridated drinking water suffer health issues and varying degrees of f uorosis.[2]

In Mexico, 5 million people (approximately 6% of the population) are affected by f uoride as a result of drinking groundwater,[2] often hydrothermal groundwater characterized by containing potentially toxic chemical elements, including F, and concentrations of up to 6.8 ppm have been detected. It is worth mentioning that the W orld Health Organization (WHO) recommends a concentration of 0.7 ppm for drinking water.[2]

The aim of this review is to set out information regarding the toxic potential of F and its effects on the nervous system, with special attention to populations exposed to the intake of this mineral at concentrations outside of f cial guidelines.

Development

The main route for the incorporation of F into the human body is the digestive tract; 90% of the F ingested is absorbed in the stomach. In adults, some 10% of it is deposited in the bones, whereas in children, up to 50% is f xed to bone tissue. The maximum concentration of F in plasma is reached between 30 and 60 min after intake.[1]

In newborn children, close to 90% of the F absorbed is retained in the skeletal system. This aff nity decreases with age and stabilizes. In children, around 50% of the F absorbed is f xed to the skeleton by the time the f rst stage of development has been completed and the remaining 50% is excreted through the kidney.[1]

Fluorine is capable of crossing the blood-brain barrier ,[3] which can cause biochemical and functional changes in the nervous system during pregnancy since F accumulates in the brain tissue prior to birth.[4] Exposure to F during embryonic development has been reported to be related to learning disorders.[5] In this sense, other research mentions the consumption of large amounts of F as associated with decreased intelligence in children. [6] Studies carried out to evaluate the toxicity of F on neurodevelopment during pregnancy have demonstrated signi f cant differences in neurobehavioural performance in newborns in areas that

are endemically rich in F compared to controls when assessing visual and auditory orientation reactions.[7] On the other hand, the levels of neurotransmitters such as norepinephrine, 5-hydroxytriptamine, and their receptors have been found to be decreased in the brain of aborted foetuses in areas that present cases of endemic fluorosis, while the level of epinephrine is higher than the concentrations found in subjects from areas where this problem does not occur. Hence, these results suggest that the accumulation of F in brain tissue can disrupt the synthesis of certain neurotransmitters and receptors in cells of the nervous system and may even go so far as to provoke neural dysplasia or other damage. [8] Likewise, F has been reported to have a specific effect on protein synthesis in the brain, entailing degenerative changes in the neurons, varying degrees of loss of grey matter, and changes in Purkinje cells in the cerebellar cortex;[9] moreover, it causes swelling of the mitochondria, granular endoplasmic reticulum, chromatin clumping, damage to the nuclear membrane, and a decrease in the number of synapses, mytochondria, microtubules, and synaptic vesicles, as well as damage at the synaptic membrane level. These changes indicate that F can delay cell growth and division in the cortex, and that the reduced number of mytochondria, microtubules, and vesicles in the synaptic terminal may reduce efficiency in neuronal connections and give rise to abnormal synaptic functioning and impact cognitive development during postnatal life.[4] Likewise, these changes might account for some of the neurological alterations present in patients with skeletalfluorosis, such as numbness in arms and legs, muscle spasms and pain, tetanus-like convulsions, and spastic paraplegia. [2] On the other hand, exposure to F increases the production of free radicals in the brain by activating different metabolic pathways related to Alzheimer's disease. On the experimental level, F has been seen to have an inhibitory effect on free fatty acids, in the brains of both male and female rats, [9] in addition to significant changes in the morphology of the hippocampus, the amygdala, the cortex, and the cerebellum.[10,11]

In this regard, animal studies have yielded information about the direct toxic effects of fluoride on brain tissue, including: decreased number of acetylcholine (ACh) receptors, lower lipid content, damage to the hippocampus and Purkinje cells, increased formation ofβ-amyloid plaques (classic cerebral anomaly in patients presenting Alzheimer's disease), exacerbation of lesions caused by iodine deficit, and accumulation of fluoride in the pineal gland.[12,13]

On the other hand, in studies using experimental models, the offspring of rats given a dose of 5, 15, or 50 ppm of F in their drinking water during gestations and lactation were seen to exhibit significantly high levels of the enzyme acetylcholinesterase 80 days after birth. The high activity of acetylcholinesterase might lower ACh levels and, given that said enzyme degrades the neurotransmitterACh, it has an important impact on brain development.[14,15] ACh plays a part in regulating several different functions, such as the transition from sleep to wakefulness and processes that have to do with learning and memory, among others. At the level of the brain, there are precise mechanisms regulating its synthesis and release, which is important insofar as changes in the concentration of any neurotransmitter during development may have permanent neurological consequences that manifest in adulthood.[11]

Both learning and memory have been reported to be altered in mice treated with fluorinated water. The ability to learn has been found to be decreased in subjects who drink water with high concentrations of F in comparison with those who drink water containing a lower concentration of this element.[15]

Some studies performed in individuals who have been chronically exposed to F due to industrial contamination report that they have difficulties concentrating; certain aspects of their memory are altered, and they suffer fatigue and general malaise.[16]

For their part, studies carried out with humans in China shoed that a concentration of 3-11 ppm of fluoride in drinking water affects the functioning of the nervous system without causing physical malformations. The intelligence quotient (IQ) was assessed in children in communities in which there is a high degree of exposure to F (4-12 ppm) and it was found to be significantly lower than that of children living in communities with concentrations of close to 0.91 ppm.[6]

Another study conducted in children aged 6 to 8 years found poor visual spatial organization, which can affect reading and writing abilities; moreover, a concentration of 4.3 mg/creatinine was recorded in urine. In this regard, there have been reports that the levels of this chemical element are also high in the urine of people who drink water containing a high F content, which suggests that there is a relationship between the intake of F in drinking water, the concentration of F excreted in urine, and IQ.[17]

Some researchers suggest that the adequate intake of iodine might treat or counteract the toxic effect of F on the brain and IQ. On the other hand, in research performed in animals, a partial recovery has been seen in all the parameters studied when exposure to F is withdrawn; nevertheless, this recovery with respect to the toxic effects is more complete when ascorbic acid, calcium, or vitamin E are administered either individually or in combination, although recovery has been shown to be more effective with combination therapy.[18] Nonetheless, more studies are needed in this regard.

Conclusion

Fluorine is a chemical element found in high concentrations in the earth's crust. In many countries where the main source of drinking water is hydrothermal, F concentrations exceed those contemplated by the corresponding official regulations. Until now, the reports pose interesting controversies as to the role F plays in health. However, there are data showing that F has toxic effects on the central nervous system, depending on the dose administered, age, and exposure time; hence, it is recommended that the geographical location of a given population and the quality of the water they drink should be taken into consideration so as to take preventive measures for its use and, in areas where the fluoride concentration exceeds 0.7 mg/L, to avoid the intake of the drinking water, fluorinated salt, and the use of toothpastes and articles containing F.

Conf icts of interest

The authors declare no conf ict of interest.

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