FLUORIDE
Quarterly reports

Fluoride-Induced Stress in Relation to Brain Health

Unique digital address (Digital object indentifier[DOI} equivalent):
https://www.fluorideresearch.online/epub/files/252.pdf

Ramesa Shafi BHAT[1], Rajesh SINGH[2], Abdul Majid BHAT[3] ,Sooad Al-DAIHAN[1]

[1] Biochemistry Department, Science College of King Saud University, Saudi Arabia

[2] School of Applied Science, Shri Venkateshwara University, Gajraula, Uttar Pradesh, India
[3] Department of Information Technology, Central University of Kashmir, Ganderbal, Jammu &Kashmir, India

***Corresponding author:**
Dr. Ramesa Shafi Bhat
Biochemistry Department, Science College of King Saud University, PO Box 22452, Zip code 11495, Riyadh, Saudi Arabia
E-mail:rbhat@ksu.edu.sa

Accepted: 2023 Nov 19
Epub as e252: 2024 Jan 1

ABSTRACT
Fluoride has been added not only to drinking water but also in dental products, drugs, and infant formulas in many countries for public health however, its risks remain a primary topic worldwide. Fluoride can accumulate in the animal/human body, and its long-term exposure harms body tissues, particularly the nervous system without causing any visible deformities before. It rapidly passes the blood-brain barrier and affects cellular energy metabolism, the production of inflammatory mediators, the metabolism of neurotransmitters, the activation of microglia, and the expression of proteins involved in the maturation of neurons. Fluoride induces apoptosis and inflammation in the central nervous system is reported as the main reason behind its toxicity. With aluminum, it forms a fluoroaluminum complex that can accumulate in the brain for prolonged neurotoxicity Fluoride increases intestinal inflammation and permeability and decreases mRNA levels of tight junction proteins in the intestines resulting in brain-derived injury through the gut-brain axis. Although there are many mechanisms involved in the neurotoxic effects of fluoride, but its exposure through various sources on brain health need to be elucidate through well designed animal models and epidemiological studies.

Key-words: Fluoride; oxidative stress; neuroinflammation; gut health

INTRODUCTION

Fluoride at large concentrations is an environmental pollutant that has a negative impact on ecosystems [1]. On Earth, fluorine is hardly found in its elemental form, although it is prevalent in the ecosphere as a fluorine compound [2]. Health risks associated with fluoride have been noted for populations living in industrialized areas [3-4]. Fluoride levels in the soil and water are higher in certain places as a result of anthropogenic emissions. These consist of industrial air pollution deposits, insecticides, and fertilizers [5]. Plants and animals store the fluorides that are present in the soil, air, and water. Food and drinking water are therefore the main sources of fluoride intake in humans. In addition to these, there are few other sources like dental products mainly toothpaste and mouth rinses, drugs, infant formulas and fumes from industrial belt [6]. Some beverages, including tea also have high quantities of Fluorides [7]. Over the past few years, there has been a lot of discussion over fluoride toxicity against plants [8-9], animals [10-11], and even microbes [12]. Different viewpoints exist on fluorine's importance as an

element and the extent of its toxicity to people (particularly when it comes to water fluoridation). Fluoride affects the human body in two extremes. Its low level interferes with dental enamel and bone demineralization and acute and chronic exposure to elevated doses may trigger a broad spectrum of disorders [13]. Health professionals have been at odds over the possibility that fluoride in drinking water is hazardous to the developing human brain. Fluoride is first partially absorbed (about 25%) as hydrofluoric acid through the stomach, and the majority of the remaining fluoride is absorbed in the small intestine, regardless of pH. The liver and kidney then filter the absorbed fluoride to produce the final plasma fluoride concentration.

Adults exposed to extremely high fluoride levels are known to experience neurotoxicity, while rodent studies have revealed deleterious effects on learning and memory [14]. Fluorosilicic acid (H2SiF6), sodium fluorosilicate (Na2SiF6), or sodium fluoride (NaF) are the three substances that are used to fluoridate water among them fluorosilicic acid is mostly used. Small water systems also utilize sodium fluoride. The American Dental Association (ADA) advises adding 0.7 parts per million (ppm), or 0.7 milligrams per liter (mg/L), of fluoride to water [15-16]. World Health Organization acclaimed the concentration range of 0.5 to 1.0 mg/L of fluoride in water supplementation [17] The Environmental Protection Agency (EPA) only permits 4.0 mg/L of fluoride in public water systems [15-16].

A deficiency in fluoride if the intake concentration is below 0.5 mg/L causes dental caries and weakening of the bones However, repeated consumption of fluorine, if exceeds 1.5 mg/L over a long period, can result in fluorosis in humans and animals [18]. Between 40 and 80 mg/kg of sodium fluoride can cause fatal poisoning in humans [19]. Fluoride exposure is believed to have both immediate and long-term impacts, particularly at crucial stages of development. Chronic low-level fluoride exposure may cause mental health problems and intellectual deficiencies [20]. It is believed that iodine levels in the body and genetics may impact the potency of exposure. Fluoride can affect mitochondrial DNA, which has significant consequences for various mental diseases [20].

Approximately 99% of retained fluoride is bonded in calcium-rich tissues like bone and approximately 75–90% of ingested fluoride is quickly absorbed and dispersed throughout the body [21]. In addition, fluoride passes through the placenta and gets to the developing fetus and amniotic fluid. The amount of fluoride circulating in the body can be determined through analyses of urine and blood [22]. The fasting plasma-fluoride concentration is roughly equivalent to the quantity in drinking water. The adult brain may be somewhat protected from many toxins by the blood-brain barrier, but in fetuses and young children with an immature blood-brain barrier, this protection is less. Fluoride concentrations in human cerebrospinal fluid are approaching those found in serum, which is evidence that fluoride crosses the blood-brain barrier [23]. Further evidence that circulating fluoride reaches the brain comes from imaging studies of radioactive fluoride used in cancer treatment [24-26]. There is evidence that fluoride builds up in the brain regions responsible for memory and learning centers [27-29]. This review provides information on the neurotoxic potential of fluoride particularly at concentrations that are over the recommended levels by official regulations.

TRANSPORT OF FLUORIDE IN THE BRAIN

Fluoride is absorbed from the digestive tract, and its peak plasma concentrations only last for around 30 minutes. It enters the placenta and breast milk from the blood and passes through the blood-brain barrier into the brain. Fluoride is easily incorporated into calcified tissues like bone and teeth, which are most noticeable during times of rapid growth. Calcified tissues account for around 99% of the body's fluoride burden that is not quickly eliminated by urine. The blood-brain barrier does not effectively prevent fluoride from entering the neurological system [30]. The typical Cerebrospinal fluid (CSF) /blood fluoride ratio is less than 1.0. [14] Fluoride is actively transported through the blood-brain barrier which is comparable to that of other halogens and ionic chemicals. Fluoride can also cross the blood-placenta barrier in overexposed women and enter the fetal circulation [31], where it has been demonstrated to impede central nervous system development and result in neurodegeneration. Long-term exposure to

fluoride results in abnormalities in the structure of the brain's cells [32]. There are numerous studies showing animals that were exposed to high amounts of fluoride either directly or through the mother have histological abnormalities in the brain tissue. It has been demonstrated that fluoride deposition in the fetus's brain and its passage through the placenta of pregnant women with chronic fluorosis have a negative effect on brain development. [30]. Numerous enzymes that require divalent cations as cofactors are inhibited by fluoride [30-36]. The enzymes that fluoride inhibits are involved in free radical scavenging, protein and amino acid metabolism, and energy metabolism. Since it alters the metabolic pathways in the brain, fluoride is regarded as a metabolic toxin [37]. Studies on the impact of fluoride on brain metabolism have revealed that fluoride (as NaF) impairs the activities of the enzymes involved in nerve impulse transmission. Acetylcholinesterase, magnesium, calcium, and sodium-potassium ATPase activities are affected by fluoride in the brain tissue.

THE ROLE OF FLUORIDE IN THE PATHOGENESIS OF BRAIN DISORDERS

Fluoride affects cellular energy metabolism, the production of inflammatory mediators, neurotransmitters, microglial activation, and the expression of proteins involved in neuronal maturation in the brain. Fluoride induces apoptosis and inflammation in the central nervous system is reported the main reason behind fluoride toxicity-related brain disorders. Clinical manifestations of the effects of fluoride exposure on the developing brain include memory loss and cognitive process impairment. According to epidemiological research, children who were exposed to excessive fluoride had lower intelligence quotient (IQ) scores than those who were not [38]. Industrial workers who were exposed to fluoride over an extended period of time displayed a range of neuropsychiatric symptoms, such as sleepiness, difficulty focusing and learning, and memory problems [39–42]. Disrupted neuronal and glial cell metabolism is linked to fluoride-induced disorders. Fluoride buildup in the hippocampus promotes the production of reactive oxygen species (ROS) and oxidative stress resulting in neuronal degeneration [43]. Numerous studies have demonstrated that long-term exposure to high-fluoride environments (one gram per liter) can result in severe behavioral and cognitive deficits in rodents, including decreased short-term memory, delayed object recognition, impaired spatial memory retention, and neuropathological damage [40,41]. Additionally, numerous studies have demonstrated that fluorosis causes altered metabolism and oxidative stress in the brain, affects mitochondrial structure and function by obstructing the work of antioxidant enzymes, and causes cognitive impairment [44,45]. Fluoride increases intracellular calcium ions Ca^{2+} by activating calcium channels in mitochondria [46]. Calcium regulates mitochondrial function at many levels and stimulates ATP synthesis. Imbalanced mitochondrial Ca^{2+} homeostasis plays a key role in several pathologies. Ca^{2+} overload in the mitochondrial matrix results in the release of ROS species and cytochrome c leading to apoptosis [47]. Ono et al [48] reported increased activity of Ca^{2+} channel by fluoride in dose–dependent manner. Fluoride modulates the phosphorylation state of channel protein to increase the Ca^{2+}- channel activity [48]. Fluoride toxicity in the developing brain is the most challenging concern nowadays and how those effects may contribute to a decline in IQ and disruptions in learning and memory functions[41,49]. It is believed that fluoride toxicity could be involved in the etiology of neurological and neurodegenerative disorders such as Autism, Alzheimer's, and Parkinson's, fatigue, dizziness, vertigo, loss of motor coordination, and complex paralysis of arms and legs[10, 50-51].

Fluoride induced Oxidative stress

Oxidative stress is considered as one of the main mechanisms behind fluoride toxicity which is activated by imbalanced production and elimination of free radicals [49]. The brain is susceptible to excessive ROS production and oxidative damage due to its high levels of polyunsaturated fatty acids and redox-active metals (Cu and Fe) as well as its high metabolic rate, which is characterized by high oxygen consumption (20% of basal oxide consumption), and low regenerative capacity. Fluoride has a well-documented pro-oxidant action [52,53]. Fluoride causes oxidative stress and impairs the activity of antioxidants in the brain (Figure 1). Sodium fluoride exposure enhanced lipid peroxidation and decreased or raised levels of

antioxidants in the brain tissue. An increase in malondialdehyde (MDA), glutathione (GSH), glutathione S-transferase (GST), glutathione peroxidase (GSH-Px), and ascorbic acid was observed in the brain tissue of rodents after receiving fluoride [54-56]. In experiments using murine microglial BV-2 cells, Shuhua et al. demonstrated that microglial activation, which increases the production of ROS and RNS (reactive nitrogen species) and causes oxidative stress, is at least partially responsible for the toxic effects of fluoride on the nervous system [57]. This is supported by Saralakumari et al that link chronic fluoride exposure to higher levels of oxidative stress in humans [58]. Fluoride toxicity also has an impact on a number of antioxidant enzymes. Although the specific nature of this action is unclear, fluoride inhibits the activity of antioxidant enzymes. Cells treated with a high dose of NaF showed a decrease in Superoxide dismutases (SOD) activity. Rodents fed with fluoride water showed increased Cat activity which can be attributed to the activation of defense systems against the effects of excessive oxidation [59-60]. Fluoride at a dose of 20 mg/kg decreases GSH, SOD, and GPx activity in the brain tissues in rats [61]. GSH concentration was decreased in cultured rat hippocampus neurons on exposure to sodium fluoride [62].

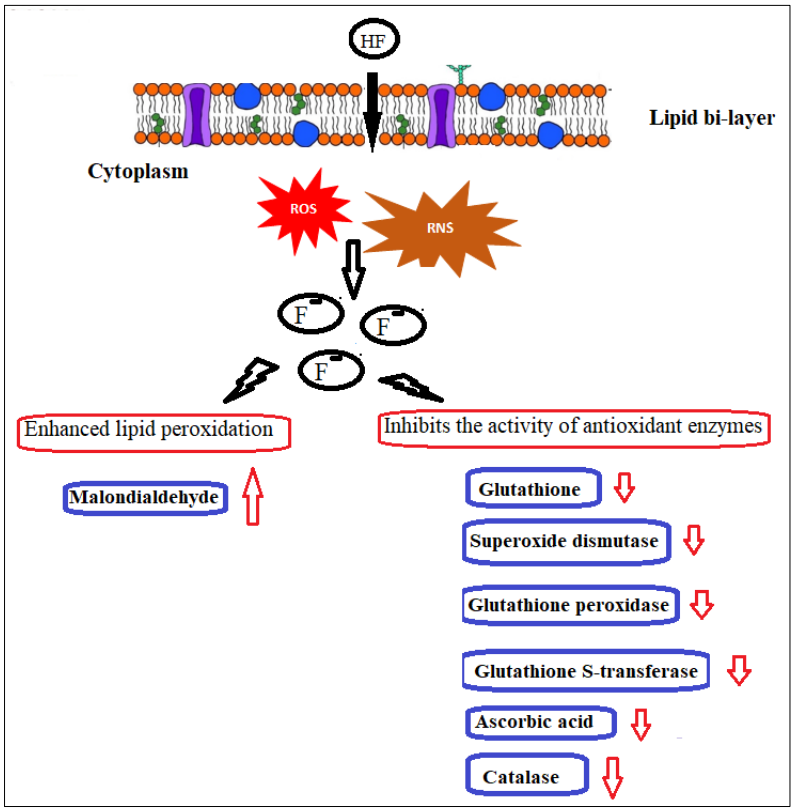

Figure 1- Fluoride toxicity results in the production of ROS (reactive oxygen species) and RNS (reactive nitrogen species) which in turn promotes lipid peroxidation and inhibits the activity of antioxidant enzymes.

Fluoride induced neuroinflammation

Inflammation has been connected to numerous brain disorders. Although it is believed that inflammation is not the cause of neurodegenerative diseases, the long-term upregulation of the inflammatory response brought on by the activation of microglia and astrocytes in such conditions raises the possibility that neuroinflammation plays a significant role in neuronal dysfunction and death [63]. Fluorine easily crosses the blood–brain barrier to induce neuro-inflammation (Figure 2). Nuclear transcription factor kB (NF-kB), a crucial transcription factor that controls the expression of genes linked to immune response, is known to be

activated by inflammation in the central nervous system [64]. NF-kB plays a significant role in inflammation brought on by the interaction of astrocytes and microglia [65,66]. It has been demonstrated that fluoride increases NF-kB activity in BV2 microglia in vitro [67]. Fluoride exposure can produce tumor necrosis factor-alpha (TNF-a) and interleukin-1 (IL-1) in the brain which can activate NF-kB [68]. Numerous effects of NF-kB activation include enhanced NO production, nitric oxide synthase activity stimulation, and cyclooxygenase 2 (COX-2) expression which plays a key role in the induction and progression of neuroinflammation. Fluoride toxicity is also linked with cytokine release and activation of macrophages and microglia as a significant source of proinflammatory factors [69].

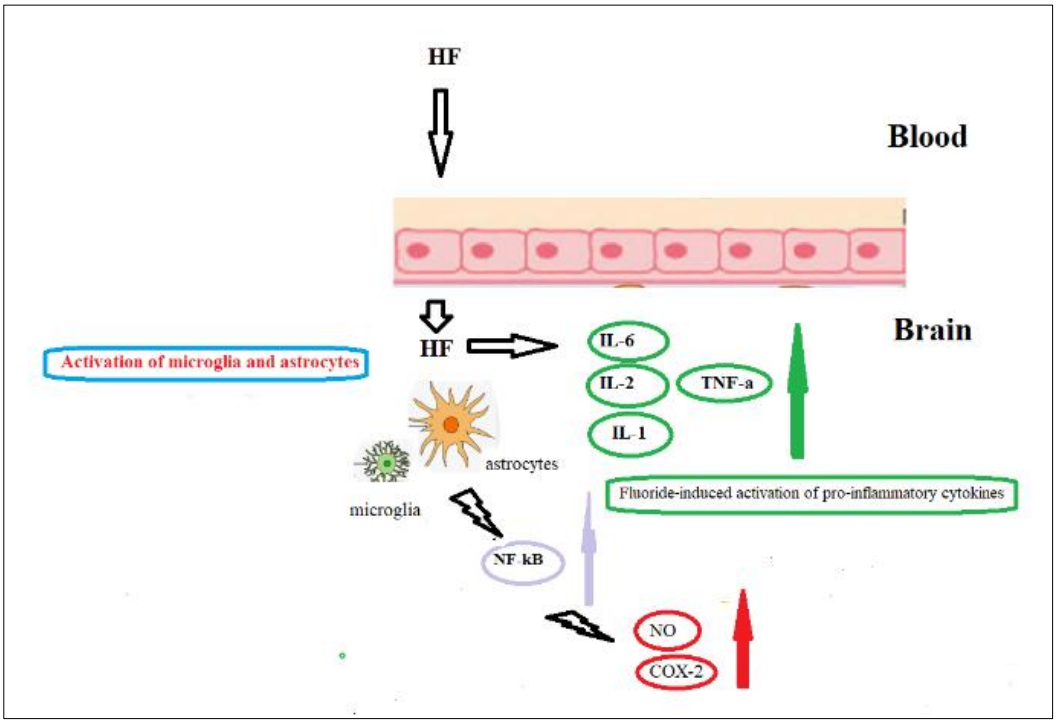

Figure 2- Fluoride crosses the blood-brain to produce an inflammatory mediator

Fluoride-induced activation of pro-inflammatory cytokines like IL-1, IL-2, IL-6, and TNF- a HeLa cells is reported [70]. Activation of microglia in the cerebral cortex and hippocampus in fluoride-treated rodent model contributed to the onset and development of by affecting the production of certain cytokines, the brain is inflamed [71]. Phospholipase A2 (PLA2) activity in macrophages is stimulated by aluminum fluoride [72]. The effect of low fluoride concentrations on PLA2 exocrine activity and subsequent eicosanoid synthesis, in particular prostaglandin E2 (PGE2) and thromboxane A2 (TXA2), suggested enhanced activity of cyclooxygenases. Arachidonic acid is released when phospholipase A2 catalyzes the hydrolysis of the ester link in the sn-2 position of glycerophospholipids, further promoting the inflammatory response [73]. In consequence, PLA2 activation and a rise in free arachidonic acid promote the production of pro-inflammatory eicosanoids in macrophage cells [74].

Recently, Reddy *et al* [75] studied the neurological changes in NaF-exposed Wistar rats. The study reported a dose-dependent increase in the levels of the neurotransmitters glutamate, adrenaline, histamine, and serotonin as well as neuroinflammatory mediators (COX-2, VEGF, HSP-70, PKC, TNF-, and iNOS). The ultrastructural alterations seen in the neocortex, hippocampus, and cerebellum, as well as the spinal cord and sciatic nerve, further confirm the neurodegenerative changes brought on by NaF. According to these findings, high fluoride levels cause neuroinflammatory reactions that culminate in neuropathological alterations in the brain. Wang et al [76] reported fluoride-induced ferroptosis and inflammation in the brain cells. Fluoride can increase

neuronal cell inflammation by causing neutrophil extracellular traps (NETs). Fluoride causes an imbalance in neutrophil calcium, which in turn permits L-type calcium ion channels (LTCC) to open and allows extracellular free iron to enter the cell, resulting in neutrophil ferroptosis and inflammation. Cerebrovascular dysfunction is promoted through excessive production of NETs [76] and subsequent effects brain inflammation.

Fluoride induced Neuro-apoptosis

Apoptosis plays a major role in the maintenance and advancement of physiological processes, such as tissue homeostasis, aging, healing, and embryogenesis. [77]. Apoptosis pathways protect the body from aberrant or mutant cells under physiological conditions which otherwise results in uncontrolled cell proliferation and oncogenesis [78]. Excessive apoptosis contributes to the etiology of neurodegenerative illnesses triggered by many environmental factors including fluoride [78].

In vitro research on rat hippocampus neurons revealed enhanced NF-B expression and a higher percentage of apoptotic cells after sodium fluoride treatment [79]. In addition, fluoride was shown to have an effect on apoptosis in vitro studies performed on SH-SY5Y neuroblastoma cells. Fluoride increased the expression levels of caspase-3, and caspase-8 (Figure 3) [80]. Similar to this, Liu et al. revealed in vivo the potential proapoptotic effects of fluoride by showing that fluoride-exposed rats had an increased number of apoptotic brain cells [81]. The pro-apoptotic impact of fluoride may also be mediated by the activation of Jun N-terminal kinases (JNK) through phosphorylation resulting in caspase activation (Figure 3) [82]. Fluoride increases the expression levels of proapoptotic Bax protein and decreases the expression of antiapoptotic Bcl-2 protein in rodents [71] An increase in apoptotic processes in brain structures of fluoride-treated rodents was detected in an analysis using the terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) method.

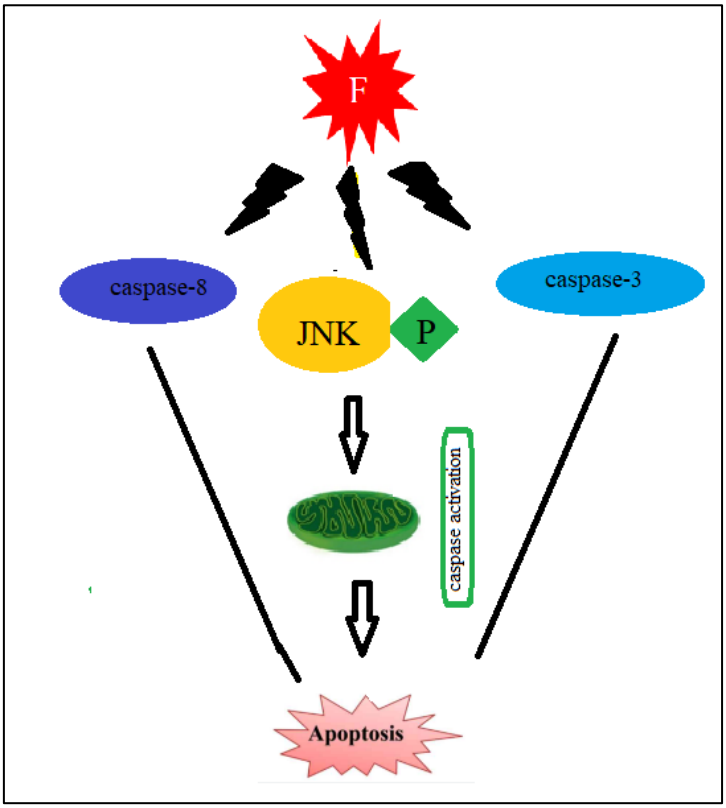

Figure 3- Fluoride-induced apoptosis in brain cells.

Fluoride-induced glutamate excitotoxicity.

Excitotoxicity is among the main mechanisms involved in a wide range of neurological disorders, including

strokes, brain injuries, central nervous system (CNS) infections, autoimmune diseases, multiple sclerosis, heavy metal toxicity, brain tumors, and the majority of neurodegenerative diseases, including Alzheimer's dementia, Parkinson's disease, and autism [83,84]. Although it seems that fluoride toxicity is secondary to many unrelated processes, there is strong evidence that excitotoxicity may be a central mechanism [84]. In this process, acidic amino acids such as neurotransmitters glutamate and aspartate in addition to homocysteine, cysteine, cysteine sulfinic acid, cysteic acid, and cysteine accumulate in the synaptic cleft. Several glutamate receptors on the postsynaptic membrane are typically activated by the neurotransmitters glutamate and aspartate, which cause neuronal excitement. In fact, glutamate, which regulates learning, alertness, and attention, is the most prevalent neurotransmitter in the CNS but most neurotoxic [85]. Glutamate is supplied to the organism with the diet but, only a little is passed through the blood–brain barrier because of a protective mechanism against the excessive inflow of it in the brain which can otherwise cause depolarization and damage the neurons [85]. Many enzymatic pathways are involved in maintaining adequate extracellular glutamate levels once released into the synaptic cleft [86]. Some studies have reported a decrease in Glutamate levels in the cortex and hippocampus in rodents on exposure to Fluorine through drinking water [86.88]. Fluoride exposure is also reported to impair the activities of Glutamate metabolism-related enzymes such as glutamic acid decarboxylase glutamate oxaloacetate and glutamate pyruvate transaminases in hippocampus [88-90]. Fluoride when builds up in the brain causes a variety of abnormalities in learning and memory and decreases synaptic cleft width. Excessive fluoride may increase the susceptibility of neurons to excitotoxicity by producing free radicals and lipid peroxidation, which may harm synapses and cause damage to neurons [91]. Glutamate the most prevalent and significant excitatory neurotransmitter in the CNS has a role in the plasticity of neural networks and processes linked to ontogeny, memory, and learning [92]. However, excessive glutamatergic system activation can result in excitotoxicity [93]. The clearance of extracellular glutamate, which is primarily mediated by sodium-dependent transport into astrocytes, is a crucial factor in the physiologic/excitotoxic tone of the glutamatergic system, which affects other neurotransmission systems [94]. Evidence regarding the cholinergic system has demonstrated that fluoride toxicity can affect cholinergic neurotransmission. High doses of fluoride reduce nicotinic acetylcholine (ACh) receptors and alter the histopathology of brain cells [95]. The neurotoxicity of fluoride is thought to be primarily caused by excitotoxicity caused by microglial activation (Figure 4) [96]. It is a common mechanism that has been linked to numerous neurological disorders as well as the neurotoxic effects of various chemicals and heavy metals. Excitotoxicity is brought on by excessive glutamate receptor stimulation in neurons, which activates the brain's immune cells called microglia and causes them to release cytokines and other immune proteins, ultimately leading to the death of brain cells (Figure 4). Due to the brain's defective glutamate transporters, glutamate builds up and is overstimulated by the glutamate receptors. Reactive oxygen species (ROS) and reactive nitrogen species (RNS), may also be the cause of the excitotoxicity cascade. Blaylock presented the hypothesis of excitotoxicity as the main mechanism underlying fluoride [96]. Numerous investigations on animals have demonstrated that fluoride causes histological abnormalities in the hippocampus, dentate gyrus, superficial amygdala, cortex, and cerebellum [97-99]. There are several glutamate receptors in these regions. The primary mediators of excitotoxicity are known to be produced in the brain as a result of fluoride exposure. Fluoride sets off a series of molecular reactions via G protein-coupled receptors, second messenger systems such as cAMP, cGMP, and phosphoinositides, as well as through the activation of protein kinase C, which in turn stimulates the microglial activation processes.

Fluoride enhances aluminum absorption from gastric mucosa and its penetration through the blood-brain barrier[100-101]. Fluoride can easily combine with aluminum to generate a Fluoroaluminum complex that is toxic to neurons at low concentrations and can function as an activator of G-proteins, the membrane receptor for second messenger activation [102]. Fluoride present in drinking water can increase aluminum levels in the brain resulting in glutamate transporter inhibition [103]. Aluminum glutamate produced in the GI tract alters the blood-brain barrier

making it impermeable to toxins that are mostly permeable [104]. Also, it increases the levels of glutamate and aluminum in the brain, which increases the risk of excitotoxicity. The Fluoroaluminum complex resembles phosphate groups in biological systems and can activate the G-proteins in cell membranes. It can also activate metabotropic excitatory receptors that could initiate excitotoxicity [105]. This complex can also accumulate in the brain leading to prolonged neurotoxicity causing neurodegeneration and synaptic loss. It can activate microglia to generate glutamate and quinolinic acid which are among the two powerful excitotoxins. Secretion of this excitotoxin in combination with cytokine production increases the production of free radicals. The fluctuation of glutamate levels in the brain affects many processes such as high glutamate levels pruning the synapses and dendrites, but low levels result in an excess of unneeded connections, both resulting in severe neurodevelopmental problems.

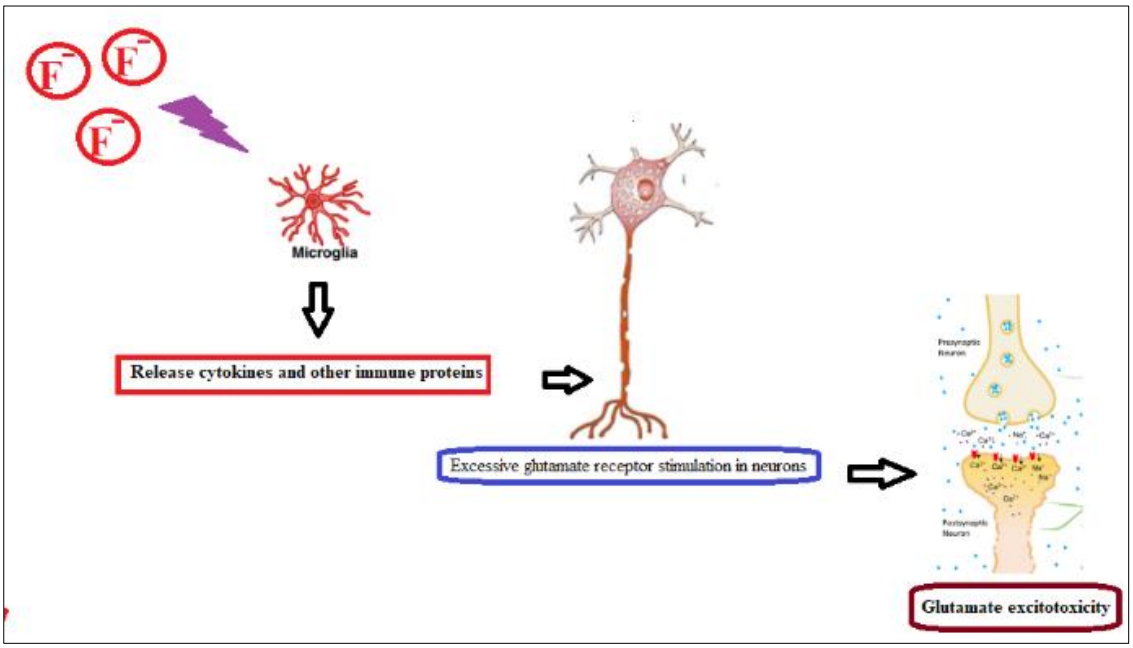

Figure 4- Fluoride toxicity through activation of microglial activation causes them to release cytokines and other immune proteins and excessive glutamate receptor stimulation in neurons results in glutamate excitotoxicity.

Fluoride and gut health

It is well known that the Gut-brain axis provides insight into brain-derived injury. Any change in the microenvironment of the intestines, like gut microbiota, inflammatory cytokines, and hormones, can affect the brain's chemistry and behavior through the gut-brain axis (Figure 5). The psychoactive effects of modulating the gut-brain axis through probiotic strain against fluoride-induced memory dysfunction in rodents are reported. It is widely acknowledged that the intestinal microbiota has a significant impact on the intestinal milieu and brain health as well. Improving the gut microbiota is a potential method to treat brain diseases and patients with disordered gut microbiota are at high risk of developing brain disorders such as anxiety, depression, learning, and memory dysfunction. Neurotoxicity caused by too much fluoride can result in memory loss, myelin loss, and neuronal loss. According to the gut-brain axis concept, the function of the brain is significantly influenced by the gut bacteria. The gut-brain axis, which connects the gut and brain, has offered new treatments for brain disorders [106]. The link between diet and gut microbiota is a major modulator behind neurodevelopmental problems [107]. A disrupted gut microbiota may be linked to memory impairment and a decrease in brain-derived neurotrophic factor (BDNF). Fluoride exposure leads to an unbalanced microbial composition (Figure 5). Fluoride exposure results in a decrease in the number

of acidogenic bacterial taxa in the gut of rodents and Lactobacillus spp. in the gut of poultry [108]. Neuroinflammation is one of the pathologies for the development of many neurodegenerative disorders [109]. Due to the high expression of cytokine receptors in the hippocampus, it is susceptible to the harm caused by inflammatory cytokines [110]. Excessive fluoride exposure led to neuroinflammation by rising TNF-a and IFN-y in the hippocampus. Fluoride increases intestinal inflammation and permeability by increasing inflammatory cytokines, serum D-lactate and diamine oxidase activity, and D-lactate concentration as well as the decreased mRNA levels of Tight junction proteins such as Zonula occludens-1(ZO-1) and occluding (Figure 5) [111].

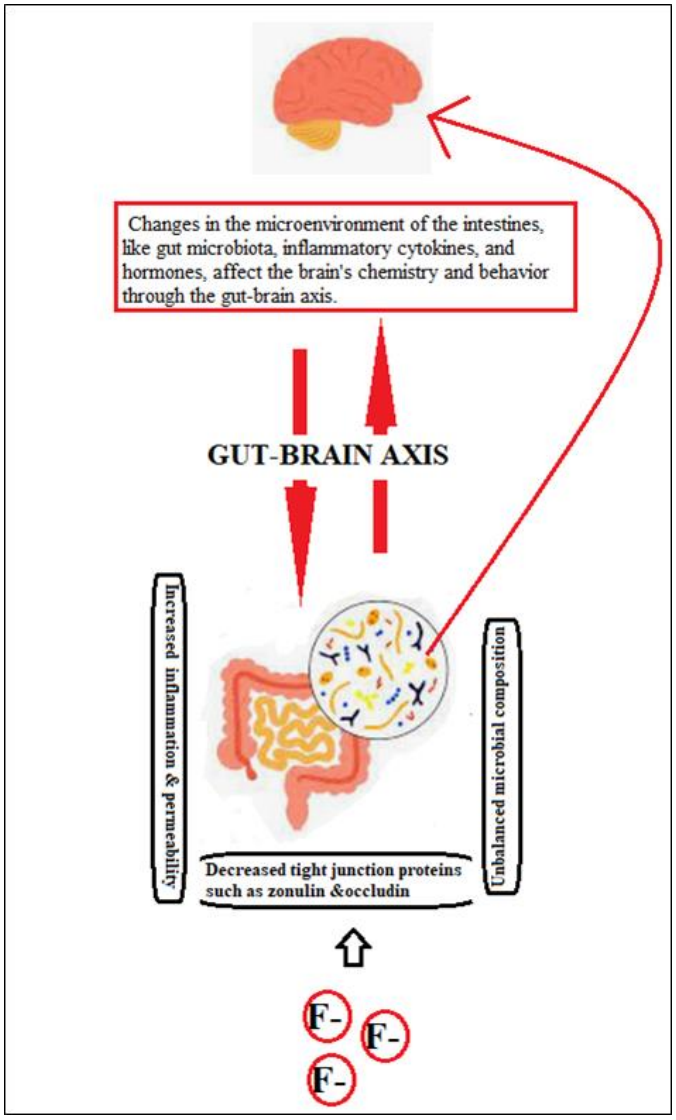

Figure 5- Fluoride exposure leads to an unbalanced microbial composition; increases intestinal inflammation and permeability; and decreases Tight junction proteins resulting in brain damage through the gut-brain axis.

CONCLUSIONS

Fluoride can be dangerous if its intake exceeds the recommended limit. Fluoride deficiency is very rare in humans as they obtain the recommended dose through food and oral hygiene products. Long-term fluoride exposure can be harmful to the human brain

which needs to be monitored carefully. The main mechanism behind its toxicity is not fully understood but various pathways related to oxidative stress and neuroinflammation may be involved. Fluoride-induced stress needs to be evaluated through animal models and epidemiological studies in order to gain a comprehensive picture of fluoride toxicity related to mental health.

FUNDING

Not applicable

CONFLICT OF INTERESTS

None

REFERENCES

[1] [1] [Zuo H, Chen L, Kong M, et al. Toxic effects of fluoride on organisms. Life Sci. 2018;198:18-24. doi:10.1016/j.lfs.2018.02.001

[2] Han J, Kiss L, Mei H, Remete AM, Ponikvar-Svet M, Sedgwick DM, Roman R, Fustero S, Moriwaki H, Soloshonok VA. Chemical Aspects of Human and Environmental Overload with Fluorine. Chem Rev. 2021 Apr 28;121(8):4678-4742. doi: 10.1021/acs.chemrev.0c01263. Epub 2021 Mar 16. PMID: 33723999; PMCID: PMC8945431.

[3] Dar FA, Kurella S .Fluoride in drinking water: An in-depth analysis of its prevalence, health effects, advances in detection and treatment,Materials Today: Proceedings, 2023

[4] Kanduti D, Sterbenk P, Artnik B. FLUORIDE: A REVIEW OF USE AND EFFECTS ON HEALTH. Mater Sociomed. 2016 Apr;28(2):133-7. doi: 10.5455/msm.2016.28.133-137. Epub 2016 Mar 25. PMID: 27147921; PMCID: PMC4851520.

[5] Lubojanski A, Piesiak-Panczyszyn D, Zakrzewski W, Dobrzynski W, Szymonowicz M, Rybak Z, Mielan B, Wiglusz RJ, Watras A, Dobrzynski M. The Safety of Fluoride Compounds and Their Effect on the Human Body-A Narrative Review. Materials (Basel). 2023 Jan 31;16(3):1242. doi: 10.3390/ma16031242. PMID: 36770248; PMCID: PMC9920376.

[6] Saad H, Escoube R, Babajko S, Houari S. Fluoride Intake Through Dental Care Products: A Systematic Review. Front Oral Health. 2022 Jun 10;3:916372. doi: 10.3389/froh.2022.916372.

[7] Satou R, Oka S, Sugihara N. Risk assessment of fluoride daily intake from preference beverage. J Dent Sci. (2021) 16:220–8. 10.1016/j.jds.2020.05.023

[8] Bhat RS, Alghamdi JM, Aldbass AM, Aljebrin NA, Alangery AB, Soliman DA, Al-Daihan S Biochemical and FT-IR profiling of Tritium aestivum L. seedling in response to sodium fluoride treatment. Fluoride 2022; 55 (1): 81-89.

[9] Bhat RS , Aldbass AM, Alghamdi JM, Alonazia MA, Al-Daihana S Trigonella foenum-graecum L seed germination under sodium halide salts exposure. Fluoride 2023; 56(2):169-179

[10] Al-Daihan S, Ben Bacha A, El-Ansary A, Bhat RS Prenatal bee pollen treatment improves the neurotoxicity in newborn rats during chronic fluoride exposure in relation to propionic acid-induced rodent models of autism. Fluoride 2020;53(1):11-22

[11] Al-Daihan S, Bhat RS Protective Effect of Bee Pollen Against Sodium Fluoride Induced Hepatonephrotoxicity and Serum Electrolyte Changes in Rats. Fluoride 2019; 52(1) 9-17

[12] Bhat RS, Soliman DA, Al-Daihan S. Sodium fluoride induces oxidative stress in oral bacteria by altering glutathione (GSH) and glutathione S transferase (GST) activity. Fluoride 2021; 54 (1):90-96

[13] Ullah R, Zafar MS, Shahani N. Potential fluoride toxicity from oral medicaments: A review. Iran J Basic Med Sci. 2017 Aug;20(8):841-848. doi: 10.22038/IJBMS.2017.9104. PMID: 29085574; PMCID: PMC565146

[14] Adkins EA, Brunst KJ. Impacts of Fluoride Neurotoxicity and Mitochondrial Dysfunction on Cognition and Mental Health: A Literature Review. Int J Environ Res Public Health. 2021 Dec 7;18(24):12884. doi: 10.3390/ijerph182412884. PMID: 34948493; PMCID: PMC8700808.

[15] Boehmer TJ, Lesaja S, Espinoza L, Ladva CN. Community Water Fluoridation Levels To Promote Effectiveness and Safety in Oral Health - United States, 2016-2021. MMWR Morb Mortal Wkly Rep. 2023 Jun 2;72(22):593-596. doi: 10.15585/mmwr.mm7222a1. PMID: 37261997; PMCID: PMC10243485.

[16] Ismail AI, Hasson H. Fluoride supplements, dental caries and fluorosis: a systematic review. J Am Dent Assoc. 2008;139(11):1457–1468.

[17] Guidelines for Drinking-Water Quality: Fourth Edition Incorporating the First Addendum. WHO Guidelines Approved by the Guidelines Review Committee. Geneva, Switzerland: World Health Organization; 2017.

[18] Ahmad S , Singh R, Arfin T, Neetia K.Fluoride contamination, consequences and removal techniques in water: a review Environ. Sci.: Adv., 2022,1, 620-661

[19] Guth S, Hüser S, Roth A, Degen G, Diel P, Edlund K, Eisenbrand G, Engel KH, Epe B, Grune T, Heinz V, Henle T, Humpf HU, Jäger H, Joost HG, Kulling SE, Lampen A, Mally A, Marchan R, Marko D, Mühle E, Nitsche MA, Röhrdanz E, Stadler R, van Thriel C, Vieths S, Vogel RF, Wascher E, Watzl C, Nöthlings U, Hengstler JG. Toxicity of fluoride: critical evaluation of evidence for human developmental neurotoxicity in epidemiological studies,

animal experiments and in vitro analyses. Arch Toxicol. 2020 May;94(5):1375-1415. doi: 10.1007/s00204-020-02725-2. Epub 2020 May 8. PMID: 32382957; PMCID: PMC7261729.

[20] Gopu BP, Azevedo LB, Duckworth RM, Subramanian MKP, John S, Zohoori FV. The Relationship between Fluoride Exposure and Cognitive Outcomes from Gestation to Adulthood-A Systematic Review. Int J Environ Res Public Health. 2022 Dec 20;20(1):22. doi: 10.3390/ijerph20010022. PMID: 36612346; PMCID: PMC9819484.

[21] Levy SM, Warren JJ, Phipps K, Letuchy E, Broffitt B, Eichenberger-Gilmore J, Burns TL, Kavand G, Janz KF, Torner JC, Pauley CA. Effects of life-long fluoride intake on bone measures of adolescents: a prospective cohort study. J Dent Res. 2014 Apr;93(4):353-9. doi: 10.1177/0022034514520708. Epub 2014 Jan 27. PMID: 24470542; PMCID: PMC3957342.

[22] Castiblanco-Rubio GA, Martinez-Mier EA. Fluoride Metabolism in Pregnant Women: A Narrative Review of the Literature. Metabolites. 2022 Apr 2;12(4):324. doi: 10.3390/metabo12040324. PMID: 35448511; PMCID: PMC9032535.

[23] Strazielle N., Ghersi-Egea J.-F. Physiology of Blood–Brain Interfaces in Relation to Brain Disposition of Small Compounds and Macromolecules. Mol. Pharm. 2013;10:1473–1491. doi: 10.1021/mp300518e.

[24] Gori S, Inno A, Lunardi G, Gorgoni G, Malfatti V, Severi F, Alongi F, Carbognin G, Romano L, Pasetto S, et al. 18F-sodium fluoride PET-CT for the assessment of brain metastasis from lung adenocarcinoma. J Thorac Oncol. 2015;10(8):e67–e68. doi: 10.1097/JTO.0000000000000523.

[25] Jones RP, Iagaru A. 18F NaF brain metastasis uptake in a patient with melanoma. Clin Nucl Med. 2014;39(10):e448–e450. doi: 10.1097/RLU.0000000000000371.

[26] Salgarello M, Lunardi G, Inno A, Pasetto S, Severi F, Gorgoni G, Gori S. 18F-NaF PET/CT imaging of brain metastases. Clin Nucl Med. 2016;41(7):564–565. doi: 10.1097/RLU.0000000000001186.

[27] Wu J, Zhu H, Ji H. Unexpected detection of brain metastases by 18F-NaF PET/CT in a patient with lung cancer. Clin Nucl Med. 2013;38(11):e429–e432. doi: 10.1097/RLU.0b013e31828162ae.

[28] Bhatnagar M, Rao P, Sushma J, Bhatnagar R. Neurotoxicity of fluoride: neurodegeneration in hippocampus of female mice. Indian J Exp Biol. 2002;40(5):546–554.

[29] Pereira M, Dombrowski PA, Losso EM, Chioca LR, Da Cunha C, Andreatini R. Memory impairment induced by sodium fluoride is associated with changes in brain monoamine levels. Neurotox Res. 2011;19(1):55–62. doi: 10.1007/s12640-009-9139-5

[30] Żwierełło W, Maruszewska A, Skórka-Majewicz M, Gutowska I. Fluoride in the Central Nervous System and Its Potential Influence on the Development and Invasiveness of Brain Tumours-A Research Hypothesis. Int J Mol Sci. 2023 Jan 13;24(2):1558. doi: 10.3390/ijms24021558. PMID: 36675073; PMCID: PMC9866357.

[31] Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological profile for fluorides, hydrogen fluoride, and fluorine (update) Atlanta: ATSDR; 2003

[32] Lopes GO, Martins Ferreira MK, Davis L, Bittencourt LO, Bragança Aragão WA, Dionizio A, Rabelo Buzalaf MA, Crespo-Lopez ME, Maia CSF, Lima RR. Effects of Fluoride Long-Term Exposure over the Cerebellum: Global Proteomic Profile, Oxidative Biochemistry, Cell Density, and Motor Behavior Evaluation. Int J Mol Sci. 2020 Oct 2; Sullivan WD. The in vitro and the in vivo effects of fluoride on the succinic dehydrogenase activity. Fluoride 1969; 2: 168-75.

[33] Goris J, Pijnenborg- Vercruysse L, Merlevede W. Effect of fluoride on the liver phosphorylase phosphatase. Biochimica et Biophysica Acta- Enzymol 1972; 268: 158-65.

[34] Haughen DA, Sutties JW. Fluoride inhibition of the rat liver microsomal esterases. J Biol Chem 1974; 9:2723-31.

[35] Tormanen CD. Substrate inhibition of rat liver and kidney arginase with fluoride. J Inorg Biochem 2003; 93: 243-46.

[36] Reiner JM, Tsuboi KK, Hudson PB. Acid phosphatase. IV. Fluoride inhibition of prostatic acid phosphatase. Arch Biochem Biophys 1955; 56:165-83.21(19):7297. doi: 10.3390/ijms21197297. PMID: 33023249; PMCID: PMC7582550.

[37] Vani ML, Reddy KP. Effects of fluoride accumulation on some enzymes of the brain and on the gastrocnemius muscle of mice. Fluoride 2000; 33: 17-26.

[38] Tang, Q.Q.; Du, J.; Ma, H.H.; Jiang, S.J.; Zhou, X.J. Fluoride and children's intelligence, a meta-analysis.

[39] Biol. Trace Elem. Res. 2008, 126, 115–120. [CrossRef]

[40] Spittle, B. Psychopharmacology of fluoride: A review. Int. Clin. Psychopharmacol. 1994, 9, 79–82. [CrossRef]

[41] Choi, A.L.; Sun, G.; Zhang, Y.; Grandjean, P. Developmental fluoride neurotoxicity: A systematic review and meta-analysis. Environ. Health Perspect. 2012, 120, 1362–1368. [CrossRef]

[42] Goschorska, M.; Gutowska, I.; Olszewska, M.; Baranowska-Bosiacka, I.; Olszowski, T.; Ra´c, M.; Chlubek, D. Effect of sodium fluoride on catalase activity in THP-1 macrophages. Fluoride 2015, 48, 274–282.

[43] Zhang, M.;Wang, A.; He,W.; He, P.; Xu, B.; Xia, T.; Chen, X.; Yang, K. Effects of fluoride on the expressionof NCAM, oxidative stress and apoptosis in primary cultured hippocampal neurons. Toxicology 2007, 236, 208–216.

[44] Dongmei Wang, Luyang Cao, Xiang Zhou, Gang Wang, Yilu Ma, Xueqin Hao, Hua Fan. Mitigation of honokiol on fluoride-induced mitochondrial oxidative stress, mitochondrial

dysfunction, and cognitive deficits through activating AMPK/PGC-1α/Sirt3,Journal of Hazardous Materials 2022; 437,,129381

[45] Wei M, Ye Y, Ali MM, Chamba Y, Tang J, Shang P. Effect of Fluoride on Cytotoxicity Involved in Mitochondrial Dysfunction: A Review of Mechanism. Front Vet Sci. 2022 Apr 19;9:850771. doi: 10.3389/fvets.2022.850771.

[46] Zerwekh JE, Morris AC, Padalino PK, Gottschalk F, Pak CY. Fluoride rapidly and transiently raises intracellular calcium in human osteoblasts. J Bone Miner Res. 1990;5 Suppl 1:S131-S136. doi:10.1002/jbmr.5650051320

[47] Chinopoulos, C. and Adam-Vizi, V. (2006), Calcium, mitochondria and oxidative stress in neuronal pathology. The FEBS Journal, 273: 433-450. https://doi.org/10.1111/j.1742-4658.2005.05103.x

[48] Ono K, Arita M. Mechanism of fluoride action on the L-type calcium channel in cardiac ventricular myocytes. Cell Calcium. 1999;26(1-2):37-47. doi:10.1054/ceca.1999.0050

[49] Banala RR, Karnati PR. Vitamin a deficiency: an oxidative stress marker in sodium fluoride (NaF) induced oxidative damage in developing rat brain. Int J Dev Neurosci. 2015;47(Pt B):298–303.

[50] Prystupa J. Fluorine—a current literature review. An NRC and ATSDR based review of safety standards for exposure to fluorine and fluorides. Toxicol Mech Method. 2011;21(2):103–170.

[51] Hussien HM, Abd-Elmegied A, Ghareeb DA, Hafez HS, Ahmed HEA, El-Moneam NA. Neuroprotective effect of berberine against environmental heavy metals-induced neurotoxicity and Alzheimer's-like disease in rats. Food Chem Toxicol. 2018;111:432–444.

[52] Chlubek, D. Fluoride and oxidative stress. Fluoride 2003, 36, 217–228.

[53] Gutowska, I.; Baranowska-Bosiacka, I.; Ba´skiewicz, M.; Millo, B.; Siennicka, A.; Marchlewicz, M.;Wiszniewska, B.; Machali´ nski, B.; Stachowska, E. Fluoride as a pro-inflammatory factor and inhibitor ofATP bioavailability in differentiated human THP1 monocytic cells. Toxicol. Lett. 2010, 196, 74–79. [CrossRef]

[54] Krechnaik J, Inkielewicz I. Correlations between the fluoride concentrations and the free radical parameters in the soft tissues of rats. Fluoride 2005; 38: 293-96.

[55] Basha PM, Rai P, Begum S. Evaluation of fluoride-induced oxidative stress in rat brain: a multigeneration study. Biol Trace Elem Res 2011; 142 : 623-37.

[56] Chinoy NJ, Shah SD. The biochemical effects of sodium fluoride and arsenic trioxide toxicity and their reversal in the brain of mice. Fluoride 2004; 37: 80-87

[57] Shuhua, X.; Ziyou, L.; Ling, Y.; Fei,W.; Sun, G. A role of fluoride on free radical generation and oxidative stress in BV-2 microglia cells. Mediat. Inflamm. 2012, 2012, 8.

[58] Saralakumari, D.; Rao, P.R. Red blood cell glucose metabolism in human chronic fluoride toxicity.Bull. Environ. Contam. Toxicol. 1991, 47, 834–839.

[59] Güner, S.; Uvar-Bozkurt, S.; Haznedaroˇ glu, E.; Mente¸s, A. Dental fluorosis and catalase immunoreactivityof the brain tissues in rats exposed to high fluoride pre- and postnatally. Biol. Trace Elem. Res. 2016, 174,150–157. [

[60] Pal, S.; Sarkar, C. Protective effect of resveratrol on fluoride induced alteration in protein and nucleic acidmetabolism, DNA damage and biogenic amines in rat brain. Environ. Toxicol. Pharmacol. 2014, 38, 684–699.

[61] Goschorska, M.; Baranowska-Bosiacka, I.; Gutowska, I.; Piotrowska, K.; Metryka, E.; Safranow, K.;Chlubek, D. Effect of acetylcholinesterase inhibitors donepezil and rivastigmine on the activity andexpression of cyclooxygenases in a model of the inflammatory action of fluoride on macrophages obtained from the THP-1 monocytes. Toxicology 2018, 406–407, 9–20.

[62] Zhang, M.;Wang, A.; He,W.; He, P.; Xu, B.; Xia, T.; Chen, X.; Yang, K. Effects of fluoride on the expressionof NCAM, oxidative stress and apoptosis in primary cultured hippocampal neurons. Toxicology 2007, 236,208–216.

[63] Chen, W.W.; Zhang, X.; Huang, W.J. Role of neuroinflammation in neurodegenerative diseases (Review). Mol. Med. Rep. 2016, 13, 3391–3396.

[64] Orellana, A.M.; Vasconcelos, A.R.; Leite, J.A.; de Sá Lima, L.; Andreotti, D.Z.; Munhoz, C.D.; Kawamoto, E.M.;Scavone, C. Age-related neuroinflammation and changes in AKT-GSK-3beta and WNT/beta-CATENIN signaling in rat hippocampus. Aging 2015, 7, 1094–1111. [CrossRef] [PubMed]

[65] Pugazhenthi, S.; Zhang, Y.; Bouchard, R.; Mahaffey, G. Induction of an inflammatory loop byinterleukin-1 beta and tumor necrosis factoralpha involves NF-kappa B and STAT-1 in differentiated human neuroprogenitor cells. PLoS ONE 2013, 8, e69585. [

[66] Simmons, L.J.; Surles-Zeigler, M.C.; Li, Y.; Ford, G.D.; Newman, G.D.; Ford, B.D. Regulation of inflammatoryresponses by neuregulin-1 in brain ischemia and microglial cells in vitro involves the NF-kappa B pathway. J. Neuroinflamm. 2016, 13, 237.

[67] Chen, R.; Zhao, L.D.; Liu, H.; Li, H.H.; Ren, C.; Zhang, P.; Guo, K.T.; Zhang, H.X.; Geng, D.Q.; Zhang, C.Y.Fluoride induces neuroinflammation and alters Wnt signaling pathway in BV2 microglial cells. Inflammation 2017, 40, 1123–1130.

[68] Zhang, J.; Zhu,W.J.; Xu, X.H.; Zhang, Z.G. Effect of fluoride on calcium ion concentration and expression of nuclear transcription factor kappa-B 65 in rat hippocampus. Exp. Toxicol. Pathol. 2011, 63, 407–411.

[69] Goldman, R.; Zor, U. On the mechanism of activation of PLA2 and Ptdlns-PLC by fluorine in murine macrophages. Adv. Prostag. Thromb. Leuktr. Res. 1995, 23, 93–97.

[70] Wang, H.U.; Zhou, B.H.; Cao, J.W.; Zhao, J.; Zhao, W.P.; Tan, P.P. Pro-inflammatory cytokines are involved influoride-induced cytotoxity potential in HeLa cells. Biol. Trace Elem. Res. 2017, 175, 98–102. [CrossRef]

[71] Yan, N.; Liu, Y.; Liu, S.; Cao, S.;Wang, F.;Wang, Z.; Xi, S. Fluoride-induced neuron apoptosis and expressionsof inflammatory factors by activating microglia in rats brain. Mol. Neurobiol. 2016, 53, 4449–4460.

[72] Wessel, K.; Resch, K.; Kaever, V. Aluminium fluoride enhances phospholipase A2 activity and eicosanoid synthesis in macrophages. Eicosanoids 1989, 2, 223–227.

[73] Chalimoniuk, M. Sekrecyjna fosfolipaza A2-udział w stresie oksydacyjnym i stanach zapalnych.Post¸epy Biochemii 2012, 58, 204–208. [PubMed]

[74] Gutowska, I.; Baranowska-Bosiacka, I.; Siennicka, A.; Ba´skiewicz, M.; Machali´ nski, B.; Stachowska, E.;Chlubek, D. Fluoride and generation of proinflammatory factors in human macrophages. Fluoride 2011, 44, 125–134.

[75] Reddy, Y.P., Tiwari, S., Tomar, L.K. et al. Fluoride-Induced Expression of Neuroinflammatory Markers and Neurophysiological Regulation in the Brain of Wistar Rat Model. Biol Trace Elem Res 199, 2621–2626 (2021). https://doi.org/10.1007/s12011-020-02362-x

[76] Wang D, Yin K, Zhang Y, Lu H, Hou L, Zhao H, Xing , Fluoride induces neutrophil extracellular traps and aggravates brain inflammation by disrupting neutrophil calcium homeostasis and causing ferroptosis, Environmental Pollution, 331, 1, 2023, 121847,https://doi.org/10.1016/j.envpol.2023.121847.

[77] Hollville E, Romero SE, Deshmukh M. Apoptotic cell death regulation in neurons. FEBS J. 2019 Sep;286(17):3276-3298. doi: 10.1111/febs.14970.

[78] Jan R, Chaudhry GE. Understanding Apoptosis and Apoptotic Pathways Targeted Cancer Therapeutics. Adv Pharm Bull. 2019 Jun;9(2):205-218. doi: 10.15171/apb.2019.024. Epub 2019 Jun 1. P

[79] Zhang, M.; Wang, A.; Xia, T.; He, P. Effects of fluoride onDNA damage, S-phase cell cycle arrest and the expression of NFkappaB in primary cultured rat hippocampal neurons. Toxicol. Lett. 2008, 179, 1–5.

[80] Xu, B.; Xu, Z.; Xia, T.; He, P.; Gao, P.; He,W.; Zhang, M.; Guo, L.; Niu, Q.;Wang, A. Effects of the Fas/Fas-Lpathway on fluoride-induced apoptosis in SH-SY5Y cells. Environ. Toxicol. 2011, 26, 86–92.

[81] Liu, Y.J.; Guan, Z.Z.; Gao, Q.; Pei, J.J. Increased level of apoptosis in rat brains and SH-SY5Y cells exposed to excessive fluoride—A mechanism connected with activating JNK phosphorylation. Toxicol. Lett. 2011, 204, 183–189.

[82] Dhanasekaran, D.N.; Reddy, E.P. JNK signaling in apoptosis. Oncogene 2008, 27, 6245–6251.

[83] Dong XX, Wang Y, Qin ZH. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta Pharmacol Sin. 2009 Apr;30(4):379-87. doi: 10.1038/aps.2009.24. PMID: 19343058; PMCID: PMC4002277.

[84] Blaylock RL. Excitotoxicity: a possible central mechanism in fluoride neurotoxicity Fluoride 2004;37(4):301–314

[85] Myhrer T. Neurotransmitter systems involved in learning and memory in the rat: a meta-analysis based on studies of four behavioral tasks. Brain Res Brain Res Rev. 2003;41(2-3):268–287.

[86] Niu R, Sun Z, Cheng Z, Li Z, Wang J. Decreased learning ability and low hippocampus glutamate in offspring rats exposed to fluoride and lead. Environ Toxicol Pharmacol. 2009;28(2):254–258.

[87] Daikhin Y, Yudkoff M. Compartmentation of brain glutamate metabolism in neurons and glia. J Nutr. 2000;130(suppl 4S):1026S–10231S.

[88] Jiang S, Su J, Yao S, et al. Fluoride and arsenic exposure impairs learning and memory and decreases mGluR5 expression in the hippocampus and cortex in rats. PloS One. 2014;9(4):e96041.

[89] Ge Y, Chen L, Yin Z, et al. Fluoride-induced alterations of synapse-related proteins in the cerebral cortex of ICR offspring mouse brain. Chemosphere. 2018;201:874–883.

[90] Sun Z, Zhang Y, Xue X, Niu R, Wang J. Maternal fluoride exposure during gestation and lactation decreased learning and memory ability, and glutamate receptor mRNA expressions of mouse pups. Hum Exp Toxicol. 2018;37(1):87–93.

[91] Strunecka A, Blaylock RL, Patocka J, Strunecky O. Immunoexcitotoxicity as the central mechanism of etiopathology and treatment of autism spectrum disorders: A possible role of fluoride and aluminum. Surg Neurol Int. 2018 Apr 9;9:74. doi: 10.4103/sni.sni_407_17. Erratum in: Surg Neurol Int. 2018 May 08;9:98. PMID: 29721353; PMCID: PMC5909100.

[92] Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, Hansen KB, Yuan H, Myers SJ, Dingledine R. Glutamate receptor ion channels: structure, regulation, and function. Pharmacol Rev. 2010 Sep;62(3):405-96. doi: 10.1124/pr.109.002451. Erratum in: Pharmacol Rev. 2014 Oct;66(4):1141. PMID: 20716669; PMCID: PMC2964903.

[93] Dong XX, Wang Y, Qin ZH. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta Pharmacol Sin. 2009

Apr;30(4):379-87. doi: 10.1038/aps.2009.24. PMID: 19343058; PMCID: PMC4002277

[94] Frizzo ME. The Effect of Glutamatergic Modulators on Extracellular Glutamate: How Does this Information Contribute to the Discovery of Novel Antidepressants? Curr Ther Res Clin Exp. 2019 Sep 10;91:25-32. doi: 10.1016/j.curtheres.2019.100566. PMID: 31871505; PMCID: PMC6911922.

[95] Long YG, Wang YN, Chen J, Jiang SF, Nordberg A, Guan ZZ. Chronic fluoride toxicity decreases the number of nicotinic acetylcholine receptors in rat brain. Neurotoxicol Teratol. 2002;24(6):751-757. doi:10.1016/s0892-0362(02)00273-8

[96] Blaylock RL. Fluoride neurotoxicity and excitotoxicity/microglial activation: crtitical need for more research. Fluoride 2007; 40: 89-92.

[97] Shashi A. Histopathological investigation of the fluoride-induced neurotoxicity in rabbits. Fluoride 2003 ; 36: 95-105.19.

[98] Ge Y, Ning H, Wang S, Wang J. Effects of high fluoride and low iodine on the brain histopathology in offspring rats. Fluoride 2005; 38: 127-32.

[99] Mullenix PJ, Debensten PK, Schunior A, Kernan WJ. Neurotoxicity of sodium fluoride in rats. Neurotoxicol Teratol 1995 ;17 : 169-77.

[100] Allain P, Gauchard F, Krari N. Enhancement of aluminum digestive absorption by fluoride in rats.Res Commun Mol Pathol Pharmacol 1996;91:225-31.

[101] Varner JA, Horvath WJ, Huie CW, Naslund HR, Isaacson RL. Chronic aluminum fluoride administration.I. Behavioral observations. Behav Neural Biol 1994;61:233-41.

[102] Park B, Yang YM, Choi BJ, Kim MS, Shin DM. Activation of G Proteins by Aluminum Fluoride Enhances RANKL-Mediated Osteoclastogenesis. Korean J Physiol Pharmacol. 2013 Oct;17(5):427-33. doi: 10.4196/kjpp.2013.17.5.427. Epub 2013 Oct 17. PMID: 24227944; PMCID: PMC3823956.

[103] Russ TC, Killin LOJ, Hannah J, Batty GD, Deary IJ, Starr JM. Aluminium and fluoride in drinking water in relation to later dementia risk. Br J Psychiatry. 2020;216(1):29-34. doi:10.1192/bjp.2018.287

[104] Deloncle R, Guillard O, Huguet F, Clanet F. Modification of the blood-brain barrier throughchronic intoxication by aluminum glutamate. Possible role in the etiology of Alzheimer's disease. Biol Trace Elem Res 1995;47:227-33.

[105] Lan JY, Skeberdis VA, Jover T, Zheng X, Bennett MV, Zukin RS. Activation of metabotropic glutamate receptor 1 accelerates NMDA receptor trafficking. J Neurosci 2001;21:6058-68.

[106] Forsythe P, Kunze WA. 2013. Voices from within: gut microbes and the CNS. Cellular and Molecular Life Sciences 70(1):55–69 DOI 10.1007/s00018-012-1028-z.

[107] Mayer EA. 2011. Gut feelings: the emerging biology of gut-brain communication. Nature ReviewsNeuroscience 12(8):453–466 DOI 10.1038/nrn3071.

[108] Luo Q, Cui H, Peng X, Fang J, Zuo Z, Deng J, Liu J, Deng Y. 2016. Dietary high fluorine altersintestinal microbiota in broiler chickens. Biological Trace Element Research 173(2):483–491DOI 10.1007/s12011-016-0672-9

[109] Frank-Cannon TC, Alto LT, Mcalpine FE, Tansey MG. 2009. Does neuroinflammation fan theflame in neurodegenerative diseases? Molecular Neurodegeneration 4(1):47

[110] Das S, Basu A. 2008. Inflammation: a new candidate in modulating adult neurogenesis. Journal of Neuroscience Research 86(9):1199–1208 DOI 10.1002/jnr.21585.

[111] Xin J, Zeng D, Wang H, Sun N, Khalique A, Zhao Y, Wu L, Pan K, Jing B, Ni X. 2020. Lactobacillus johnsonii BS15 improves intestinal environment against fluoride-induced memory impairment in mice—a study based on the gut–brain axis hypothesis. PeerJ 8:e10125 DOI 10.7717/peerj.10125