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FLUORIDE AND BRAIN: A REVIEW

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ABSTRACT: The mammalian central nervous system is composed of the brain and spinal cord. The brain is protected by the blood-brain barrier (BBB) that allows selective traffic of substances into the brain. Fluoride is a highly toxic and reactive element. We get exposed to fluoride due to its common use in toothpaste, dental gels, non-stick pans, razor blades, *etc*. Fluoride also enters our food chain through fishes that are cultivated in water bodies, which get contaminated with fluoride from running water from farms around it. Fluoride can accumulate on our body and cause toxic effects. In the context of fluoride, it is reported that fluoride exposure causes various toxic effects in our body, including the central nervous system as well. Fluoride is known to cross the blood-brain barrier and enter our brain tissue. It interferes with the normal metabolic process of the brain, generates free radicals and causes various toxic effects therein. Fluoride has been found to be linked to various pathogenic conditions of the brain as well. In this review, we have discussed the effects of fluoride on the different parts of the brain and the remedies in use.

INTRODUCTION: Fluoride, the extremely electronegative halogen in the periodic table, is a natural contaminant that coexists as compounds with other microelements in lateritic soil and rocks percolating in groundwater and freshwater of many regions across the world. In India, many regions have been summoned as fluoride endemic. In those areas, the human population is at risk of developing fluoride toxicity and so also fluorosis [1]. Fluoride not only enters the physiological system through drinking water but also through fortified health products and food chains, including plant sources, animals, and fishes [2].

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Fluoride is usually absorbed through the gut and enters the circulation where some amount is accumulated in hard and soft tissues, remaining being excreted by the kidneys. Excess fluoride, however, accumulates in blood cells, soft tissues, and hard tissues leading to systemic disorders. Bones and teeth being maximally affected and visual change of skeletal fluorosis and dental fluorosis may be observed [3].

Soft tissues exhibit histopathological as well as functional alterations probably because of fluoride mediated free radical generation, buckling of antioxidant enzyme activities, and second messenger pathway interference, ultimately leading to cellular damage and death. It is well known that vital organs such as liver, kidneys, lungs, heart, including coronary arteries, are some important sites of high fluoride accumulation [4]. However, the brain has now also been recognized as an organ for high fluoride build-up [5].

Effects of Fluoride on Various Regions of Brain: Brain is badly damaged by fluoride. It is transported through the blood-brain barrier by certain active transport mechanisms. Although tissue fluid to plasma ratio of fluoride is considered 20% less than plasma, but brain fluoride accumulation has been found to be higher in case of higher fluoride exposure. Normal CSF/blood fluoride ratio has been found to be less than one [6].

Multiple studies have been carried out related to debilitating brain function upon fluoride exposure. Fluoride affects higher neural functions, especially intelligence. In experimental animals, it has been demonstrated that fluoride reduces the neuronal density that was reflected in altered motor activities in such animals [7].

In another study, chromatolysis of cerebral pyramidal neurons, clumping of granular cells, neutropil distortion, and halos appearance along with blood congestion and perivascular emptying in rat cerebral cortex was observed in fluoride-treated animals [8]. Amongst the mechanisms of fluoride-induced such damages, it may be said that fluoride crosses the blood-brain barrier and accumulates within the neurons affecting their physiological and morphological features, including ion transport [9]. In addition, the blood-brain barrier cannot prevent fluoride from entering the nervous system [10].

TABLE 1: BRAIN AREAS EFFECTED, PATHOPHYSIOLOGICAL VARIATIONS AND POSSIBLE MECHANISMS INVOLVED IN FLUORIDE TOXICITY

Brain areas affected	Pathophysiological variations	Possible Mechanisms involved
Hippocampus	degenerative changes in nerve cell bodies like involution of cell membranes, swelling of mitochondria, clumping of chromatin material in the CA3, CA4 and dentate gyrus	Increased production of MDA, the formation of advanced glycalation end products of protein and lipids which accumulates in neurons activates proinflammatory transcription factors—NF-kB initiating the inflammatory state and MAP kinases ultimately destabilizing membrane, altering its fluidity and permeability and may activate the apoptosis pathway and initiation of apoptosis
amygdala, basal ganglia (caudate and putamen)	increase in the number of NADPH-d positive neurones, increased dendritic varicosities and dendritic intersections	Glutamate receptor-dependent raised extracellular calcium assisted reactive nitrogen species and nitric oxide synthesis leading to fluoride-induced neuronal cell death
Cerebellum	reduced density of cerebellar Purkinjee cells and Bergman glial cells	homeostasis of K+ ions and glutamate turnover in cerebellum decreased leading to a fall in the neurotransmitter assisted brain functions
Cerebral cortex	reduces the neuronal density, fall in motor activities chromatolysis of cerebral pyramidal neurons, clumping of granular cells, neuropil distortion and halos appearance along with blood congestion and perivascular emptying	Fluoride accumulation in neurons leads diminishes the expression of GLUT1 responsible for the glucose uptake in the cerebral cortex, distortion in brain energy metabolism and synthesis of precursor s for nucleoside and cofactors for lipid metabolism
Medulla oblongata	Reduced total DNA and RNA content, Chromosomal aberration and loss of mitotic cycles	Free radical-mediated damaged to DNA synthetic, transcription and translational enzymes

Sodium fluoride demonstrated a significant number of degenerative changes in nerve cell bodies like involution of cell membranes, swelling of mitochondria, clumping of chromatin material in the CA3, CA4, and dentate gyrus of hippocampus [11].

The probable reasons for such changes might be due to fluoride mediated influence on Ras protein signaling cascade leading to activation of ERK protein resulting in increased outflow of Cl^- through membrane ion channels of the regional neurons thereby affecting cell volume, cellular metabolism and functioning and propagation of nerve impulse [12] as well.

Recent studies by Bhatnagar *et al.*, evidenced an increase in the number of NADPH-d positive neurons, increased dendritic varicosities and dendritic intersections in the amygdala and caudate putamen possibly by fluoride mediated glutamate receptor-dependent raised extracellular calcium assisted reactive nitrogen species and nitric oxide synthesis leading to fluoride-induced neuronal cell death [11] **Table 1**.

Studies reveal that at a moderate dose, the cerebellum of exposed animals showed a reduced density of cerebellar Purkinje cells [13]. Bergmann glial cells (BGC) essential for maintaining

homeostasis of K^+ ions and glutamate turnover in cerebellum, showed decreased life span in fluoride exposed condition, finally leading to a fall in the neurotransmitter assisted brain functions [14] **Table 1**.

Brain Metabolism and Fluoride: It is well known that glucose is the main metabolite for neuronal cells of the brain. Although, the molecular aspects involved in glucose transportation and metabolism in neural brain tissue is not very comprehensible yet it has been reported that fluoride diminishes the expression of GLUT1 responsible for the glucose uptake in the cerebral cortex and hippocampus [15] which may cause a distortion in brain energy metabolism and synthesis of precursors for nucleoside and cofactors for lipid metabolism. However Rogalska *et al*., 2017 has reported that glucose transporters proteins 1 (GLUT 1) or 3 (GLUT 3) remained unaltered in frontal cortex and striatum in fluoride exposed rats in spite of increased brain glucose uptake in these animals compared to control revealing that a compensatory increase in glucose uptake and utilization in brain may work out to manage fluoride-induced neurodegeneration and glial renewal [16].

Chronic fluorosis leads to a decrease in total proteins and phospholipid fraction of the brain. Phosphatidyl-ethanolamine, phosphatidylcholine, and phosphatidylserine fractions were reduced while cholesterol composition remains unaffected. Modifications in brains phospholipids and ubiquinone affected by chronic fluorosis might help in the progression of neurodegenerative diseases [17].

In addition, total DNA and RNA contents of the cerebral hemisphere, cerebellum, and medulla oblongata were significantly reduced in chronic fluoride exposed experimental animals. Further changes in DNA/RNA, DNA/protein, and RNA/ protein ratios reflect inhibitory action of fluoride on DNA and RNA synthesis or the process of transcription and translation that signify the possible disorder in the process of mitotic cycles and chromosomal aberrations with exposure to fluoride [18].

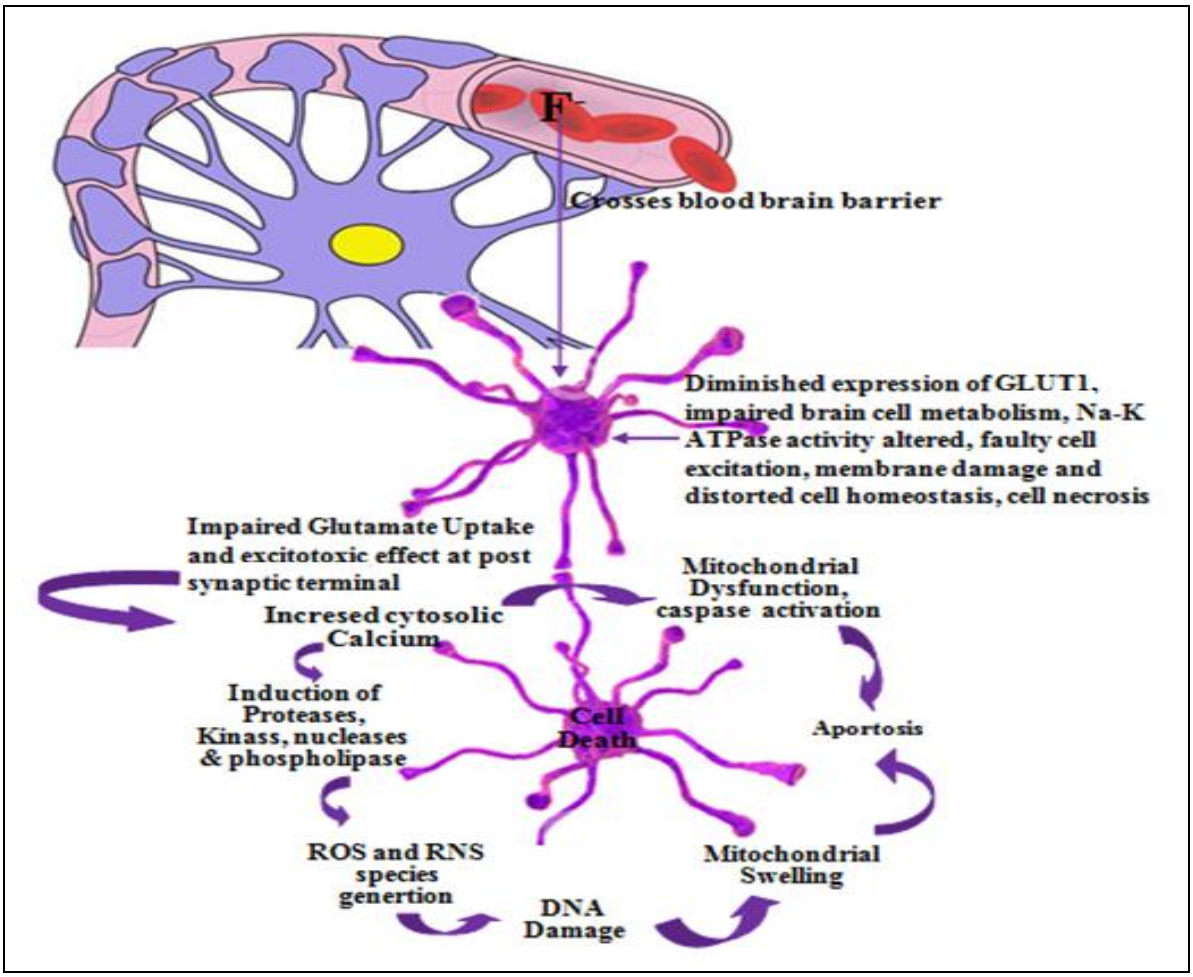

FIG. 1: EFFECTS OF FLUORIDE TOXICITY ON THE METABOLISM OF BRAIN

Fluoride has also been attributed as an enzyme poison and may bring about possible changes in enzyme systems that may lead to various diseases. Fluoride impairs the activity of membrane-bound enzymes, one such key enzyme being sodium-potassium ATPase, which is debilitated by fluoride leading to faulty membrane excitation, intracellular homeostasis, cell signaling, mitochondrial ATP production and energy metabolism [19].

Other membrane-bound enzymes interfered by fluoride are magnesium ATPase and calcium ATPase due to direct interactions of fluoride with calcium and magnesium. In addition, other enzymes like succinate dehydrogenase, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, arginase, esterase, isocitrate dehydrogenase, phosphatases, and aconitase and creatine phosphokinase in the brain showed decreased activities in rats exposed to fluoride [20]. Thus, fluoride influence the metabolism of carbohydrate, lipids, and proteins of the brain, which may indirectly affect the energy metabolism of nerves, neuro-excitation, membrane stability, and synaptic functions **Fig. 1**.

Thus, the toxic effect of fluoride may have a significant impact on the normal metabolism of the nervous tissues and thus may lead to serious impairment of the normal functions of the entire nervous system. This leads to serious pathological consequences in an individual.

Effect of Fluoride on Neurotransmitter Turnover: Experiments on animals revealed that fluoride accumulates in the areas of the hippocampus, dentate gyrus, and in the superficial areas of the amygdala, cortex and the cerebellum. One of the chief stimulating neurotransmitters in such regions of the brain is glutamates that show a reduced activity upon exposure to this element because of enhanced activity of glutamate metabolizing enzyme glutamate decarboxylase converting it into GABA (the inhibitory neurotransmitter) along with the declined activity of aspartate transaminase and alanine amino-transferase. Such alterations might change the basic neurotransmission pattern of the brain, especially the hippocampus leading to cognitive disturbances [9]. Fluoride also decreases the number of nicotinic acetylcholine receptors in brain cell culture in addition to decreased activity of acetylcholine esterase [21].

Region specific effects of fluoride on the contents of monoamines and catecholamines in brain of exposed animals have been reported. Chirumari and Reddy reported fluoride induced significant increase in the levels of dopamine, 5-hydroxy-indoleacetic acid, homovanillic acid and serotonin in the hippocampus and neocortex of the sodium fluoride treated rats; however norepinephrine and epinephrine levels were decreased in the hippocampus and neocortex of such animals. This element also impairs open-field habituation and augment noradrenaline and serotonin in the hippocampus, striatum and neocortex. Similarly elevated dopamine is also observed in striatum of fluoride exposed animals [22] whereas a gradual decrease in dopamine level was observed in both cerebral cortex and hippocampus of brains of fluoride exposed pregnant rats [23].

All such changes in neurotransmitter turnover in brain of experimental animals probably sketch out the role of fluoride in impairing higher neural functions like memory, learning and cognitive functions.

Fluoride Effects on Brain Antioxidant Milieu: Fluoride hinders electron flow through respiratory chain complex I of mitochondria leading to an increase in oxidative stress markers like reactive oxygen species, lipid peroxy and hydroperoxy radicals, oxides of nitrogen and oxidized membrane proteins. The reactive nitrogen species formed may block the enzymes of energy metabolism and destroy DNA leading to diminished intracellular enzymatic antioxidants like glutathione and interacts with superoxide radicals to form peroxynitrite. Fluoride also inhibits NADH production [25]. Further, fluoride may directly interact with metal ions of the antioxidant enzymes like catalase, GST, GPX, GR, and inhibit their activities. Thus fluoride blunts the antioxidant defense enzyme cascade in cerebral, cortex, hippocampus, cerebellum and medulla oblongata leading to increased production of MDA, the formation of advanced glycalation end products of protein and lipids which accumulates in neurons which activates pro-inflammatory transcription factors-NF-kB initiating the inflammatory state and

stimulates MAP kinases assisting membrane destabilization, altering its fluidity and permeability probably activates the apoptosis pathway followed by the initiation of apoptosis, ultimately decreases the lifespan of nerve cells [9].

Consequences of Fluoride Toxicity on Pathogenesis of Human Brain Disorders: Fluoride has a toxic effect on the brain, as reviewed above. Fluoride is known to be associated with various diseases of the brain. Studies show that fluoride exposure may lead to impairment of intelligence and adversely affects learning and memory [22, 25]. Studies have shown that exposure to sodium fluoride impairs open-field habituation and also increases serotonin (5-HT) and noradrenaline (NA) in the striatum, hippocampus, and neocortex region of the brain [22] that may be associated with the pathogenesis of Alzheimer's disease. Studies show that cellular energy metabolism, metabolism of the neurotransmitter, synthesis of inflammatory factors, etc. are affected by fluoride exposure of brain [26]. Fluoride is recognized as a developmental neurotoxin [27]. Studies reveal that intelligence in children is affected by fluoride exposure [28]. IQ has been reported to be inversely proportional to urinary fluoride level [28]. Impaired development of intelligence in children may occur due to exposure to fluoride [28].

Fluoride has been found to increase the absorption of aluminum from the intestine and across the blood-brain barrier. Fluoride and aluminum form a complex which is toxic to the neurons. A central mechanism called 'excitotoxicity' has been recognized to be involved in fluoride-induced toxicity in the CNS, including the brain. The process, 'excitotoxicity' is actually an accumulation of various neurotransmitters (acidic amino acids) in the synaptic cleft for a prolonged period which if not removed the postsynaptic neurons become over-stimulated, which causes either synaptic destruction and dendritic retraction and may even lead to the destruction of neuron by both apoptosis and necrosis [29]. Excitotoxicity is intimately associated with the free radical generation and enhanced lipid peroxidation. Hence, fluoride can initiate the process indirectly, and in chronic fluoride exposure with water fluoridation, increase in neurodegeneration-associate disorders such as Alzheimer's dementia, ALS, and Parkinson's disease may occur [29]. Fluoride has been found to affect the cognitive function of the brain [9].

Studies reveal that a number of histopathological changes in the brain, including demyelination and a decrease in the number of Purkinje cells, occurred in experimental rats chronically exposed to fluoride [30]. Studies show that chronic exposure to fluoride induces damage to the hippocampus and causes histopathological changes that resemble those associated with Alzheimer's disease [31]. Fluoride is known to accumulate in various tissues, including the nervous tissues like brain [32]. Chronic fluoride exposure has been reported to cause deleterious effects on various tissues, especially the nervous tissues. These effects have been found to be pronounced in children as they are more susceptible to the toxic effects of fluoride [32].

As fluoride can cross the blood-brain barrier, it accumulates in the brain of the embryo during pregnancy and causes biochemical and functional changes in the nervous tissues before birth. Thus, continuous exposure of the pregnant mother to fluoride may cause developmental ill effects on the embryo even before birth [33]. This exposure to fluoride during embryonic stage has been found to be related to impaired intelligence [35] and learning disorders in children [34]. Embryonic fluoride exposure and its effects on the nervous system may cause some permanent developmental damages in the nervous tissues, which may neurological changes that get reflected in adulthood [34].

Flouride accumulation in the brain may impair the synthesis of certain important proteins in the brain, including some important neurotransmitters and receptors. This may affect cell division, synapse formation, loss of gray matter, degenerative changes in the cerebral cortex, *etc.* [35, 36]

CONCLUSION: Our earlier studies reveal that fluoride-induced toxicity in liver tissue involves oxidative stress-mediated damages [39]. Other studies show that oxidative stress is involved in the pathogenesis of fluoride-induced damages in the brain and neurotoxicity effects of fluoride in experimental models [40]. Studies show that the toxic effects of fluoride on the central nervous system occur probably by activation of microglia, which

causes increased ROS and reactive nitrogen species induced oxidative stress. It was found that the concentration of MDA and contents of ROS (Reactive Oxygen Species) and $O_2^{\cdot-}$ (Superoxide anion radical) increased in sodium fluoride-treated cells [41]. Studies suggest that fluoride-induced toxicity is brought about by oxidative stress at a comparatively lower level of exposure.

Whereas etiology of fluoride toxicity at a higher level of exposure is not yet clear, and research is still in progress [40]. A multigenerational study conducted on rats exposed to a high level of fluoride (100 and 200 ppm) showed a reduced level of antioxidant enzyme activity and increased malondialdehyde levels, which might be related to oxidative damage that occurs in various specific regions of the brain [42]. Increased oxidative stress is reported in children with fluorosis [43]. Available literature shows that the administration of supplements like calcium, vitamin C, and vitamin D has caused a reduced level of serum fluoride and enhanced urinary excretion of fluoride [44]. Further, fluoride-induced neuronal oxidative stress can be ameliorated by antioxidants in developing rats [44]. Thus, fluoride-induced neurotoxicity can be fought back by combating fluoride-induced oxidative stress, which can be achieved by supplementation of various antioxidants and free radical scavenger species. Nutritional supplements have also been reported to be effective [45] and thus may help.

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