Fluoride Neurotoxicity and Mitochondrial Dysfunction

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Current animal and human research suggest that prenatal and perinatal fluoride exposure might have neurotoxic effects. Physical changes associated with fluoride exposure include fur loss and delayed reflex development in animals, intelligence loss, increased hyperactivity, and irregular moods.

Keywords: prenatal/perinatal fluoride exposure ; mitochondrial function ; neurotoxicity

1. Introduction

Fluorine is the ninth chemical on the periodic table; it is an anionic molecule that belongs to the halogen family. Fluorine is the most reactive and electronegative chemical that is currently known [1]. When fluorine acts as an ion or creates an ionic bond with another compound, it becomes known as fluoride [2]. Compounds containing fluoride exist naturally in trace amounts in human saliva, urine, and multiple tissues. Residential and industrial soil, air, and water have all been found to contain fluoride [1].

Water fluoridation occurs in the form of adding either fluorosilicic acid (H2SiF6), sodium fluorosilicate (Na2SiF6), or sodium fluoride (NaF) to the water supply. Fluorosilicic acid is the most used compound in water fluoridation. Frequently, small water systems will use sodium fluoride instead [3]. The American Dental Association (ADA) recommends adding fluoride to water at a ratio of 0.7 parts per million, or 0.7 milligrams per liter (mg/L) [4]. The maximum amount of fluoride that the Environmental Protection Agency (EPA) will allow in public water systems is 4.0 mg/L [5]. A dose of sodium fluoride that is between 40–80 mg/kg can produce lethal toxicity in humans [6]. Due to the wide range of fluoride dosing, humans may be exposed to fluoride without acute effects, and determining the potential neurotoxic effects of chronic exposure has begun to take the forefront of fluoride-based research.

Fluoride exposure is thought to have both short-term and long-term effects, especially when exposure occurs during critical points in development. Researchers are concerned that chronic low-level fluoride exposure could lead to lifelong deficits in intelligence as well as future mental health issues [7][8][9]. Moreover, concern for this exposure grows as the exact pathogenesis for fluoride exposure is not currently known. While factors such as genetics and iodine levels in the body may impact the potency of exposure impacts [7][9], more research is needed to determine exactly what leads to susceptibility. Several published articles have postulated that fluoride could be producing alterations in mitochondrial DNA; mitochondrial DNA has many implications in various mental disorders [10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28].

2. Fluoride and Neurodevelopment

2.1. Animal Studies: Cognitive Function

Sodium fluoride exposure in animals has been linked to cognitive, behavioral, and memory disruption [29]. Based on their current stage of central nervous system development, the overall consequences of fluoride exposure varied in rats/mice with more severe neurotoxic effects being observed among still-developing rats and mice compared to their adult counterparts [30][31][32]. For example, fluoride exposure during critical periods of development has a statistically significant impact on mouse cognition and behavior such as slower spatial learning, depressive tendencies, and anxious tendencies [31]. Short-term and long-term memory impairment has also been noted [29].

Researchers also found that prenatal fluoride exposure in rats was associated with hyperactivity that was comparable to that induced by amphetamines [30]. Despite the differences in hyperactivity levels, weight and plasma fluoride levels were comparable between test and control subjects [30]. Behavioral alterations were also present in mice and rats; this is thought to be due to modifications to the still-developing blood-brain barrier [30][31] as well as to effects caused by oxidative

stress [33][34]. Altogether, animal studies seem to indicate that repeated doses of fluoride can result in atypical cognitive outcomes when compared to controls.

2.2. Animal Studies: Sex Differences

The behavioral repercussions of sodium fluoride exposure in rats are also specific to sex and dose. Sodium fluoride exposure has been found to have adverse effects on learning ability and memory in rats, with more significant effects being observed among male rats [35]. In contrast, maternal sodium fluoride exposure at a low level (5–10 mg/L) was correlated with reduced anxiety in the young female rats and the adult rats compared to young male offspring. Low doses of fluoride also yielded increased hyperactivity in adult offspring born to exposed mothers [32]. Furthermore, many animal studies have linked fluoride to an increase in ADHD that is especially prevalent in males [30][31][35]. There are limited data regarding sex differences in animals that have been exposed to fluoride, and further research is needed to elucidate any potential relationships that may exist in this domain.

2.3. Animal Studies: Behavior

Fluoride exposure may also cause behavior-related effects in mice, with several studies suggesting an imbalance between nervous system excitation and inhibition depending on the dose and exposure time to fluoride [36]. Over time, fluoride-exposed mice may exhibit increased serotonin levels compared to non-exposed mice. Mice that have been exposed to fluoride have been shown to exhibit increased serotonin and brain fluoride levels at multiple time points following the exposure [37]. Serotonin (5-hydroxytryptamine [5-HT]) is a neurotransmitter that when present in the brain at inadequate levels, is heavily implicated in the development of depression and anxiety [38]. For example, 5-HT1A agonists, 5-HT1 antagonists, and 5-HT2 antagonists have been indicated for use in the treatment of many forms of anxiety disorders [39].

2.4. Human Studies: Cognitive Function and Previous Analyses

There is much debate on the topic of fluoride as a human neurotoxicant [5][6][7][40][41]. Developing brains are significantly more susceptible to neurotoxic damage from fluoride than mature brains are [9][42][43]. Children have a higher fluoride retention rate than adults; adults typically retain 50–60% of ingested fluoride, while infants and children retain approximately 80–90% [9]. This has led researchers to explore the impact that fluoride has on brain development. The first wave of manuscripts, as summarized by previously published reviews and meta-analyses, focused on cognitive outcomes, and the findings suggested that fluoride exposure can lead to a lower IQ in developing children [7][8][9].

2.5. Human Studies: Mental Health and Neurobehavior

Increased fluoride levels in tap water have been associated with increased ADHD clinical diagnoses and symptoms such as hyperactivity and inattention. However, urinary fluoride levels are not found to predict ADHD diagnoses or symptoms [44]. These data indicate that prenatal fluoride exposure may be a critical period for exposure and that it may result in delayed behavioral effects [45].

Furthermore, despite the suggestive findings among animal studies, only one human study has investigated the impact of fluoride on mental health outcomes, such as anxiety and depression, in children or adults. Statistically significant findings have associated urinary fluoride content with somatization behaviors. However, this relationship was not observed in depression- or anxiety-like behaviors, which was unexpected due to their typical comorbidity with somatization [46].

2.6. Human Studies: Sex Differences

Sex differences are also noted in some cognitive human studies of fluoride exposure, though this has not yet been widely researched. Males seem to be more susceptible to endocrine-disrupting chemicals, leading some researchers to believe that fluoride could have a more significant impact on male cognition and mental health than female cognition [8][9]. Additionally, critical windows of fluoride exposure may vary based on sex; some data indicate that the prenatal window may be more critical for males, while the infancy window may be more critical for females [42]. Males seem to show a more significantly lowered IQ than females in studies looking at equivalent maternal urinary fluoride levels in both sexes [47][6][8][48]. This trend has also been observed based on maternal fluoride intake from food [49]. However, some studies exploring sex differences saw null effects. These include studies in the U.S. and Canada.

3. Mitochondrial Dysfunction and Other Potential Pathogenesis of

Mitochondria are energy-producing, membrane-bound organelles that produce most biochemical reactions within eukaryotic cells. Mitochondria serve a variety of purposes, including regulating metabolism and apoptosis [12]. They contain a form of DNA that is known as mitochondrial DNA (mtDNA); mtDNA is primarily inherited maternally [13]. Mitochondrial DNA is known to have high rates of mutations, many of which are linked to diseases such as cancer, diabetes, and several neurodegenerative disorders [12]. While many studies of both animal and human responses to fluoride exposure have found evidence of neurotoxicity, a mechanism of this damage is not universally agreed upon. Some studies attribute an association between neurotransmitter levels and fluoride consumption to claims of neurotoxicity, others emphasize changes in neuroanatomy, and others suggest mitochondrial dysfunction as a potential mechanism.

3.1. Animal Studies: Fluoride and Mitochondrial Structure Changes

Chronic exposure to fluoride in rats can cause neuronal dysfunction and structural changes: this may alter rates of fission and fusion. Lowered levels of circulating mitochondrial fusion and fission-related particles are associated with intellectual loss in children who have been subjected to chronic fluoride exposure. Therefore, monitoring circulating mitochondria levels could provide insight into fluoride neurotoxicity and cognitive defects. Scientists must conduct more research to determine the effectiveness of this method [10]. Hippocampi that have been extracted from rats whose mothers were exposed to fluoride were found to have lower relative mtDNA levels compared to controls [15].

3.2. Animal Studies: Fluoride: Mitochondrial Damage and Neuroinflammation

There are multiple pathways of interest for researchers studying fluoride as a potential neurotoxicant. Damage to the mitochondria resulting in mitochondrial dysfunction is one mechanism that is currently under investigation. In mice, sodium fluoride concentrations of about 5 mg/L have been shown to lead to oxidative stress and the inhibition of antioxidant enzymes [14]. This leads to higher concentrations of reactive oxygen species (ROS), causing mitochondrial damage, including lipid peroxidation, mitochondrial membrane depolarization, and cell apoptosis. ROS can also result in the degradation of mtDNA [14]. Furthermore, sodium fluoride is suspected to lead to autophagy deficiency, apoptosis augmentation, compromised neuronal survival, membrane loss, increased permeability, and reduced oxidative phosphorylation in the mitochondria of rats [10].

3.3. Animal Studies: Fluoride, Neurotransmitters, and Signaling Pathways

Fluoride consumption may also impact neurotransmitter levels [16]. Serotonin levels have been shown to significantly increase in the brains of rats following fluoride exposure Notably, between 60–100 ppm of NaF, increases in serotonin have been observed at an above dose-dependent level. Glutamate and histamine levels have been shown to increase as well, while acetylcholine and dopamine levels have been shown to decrease. Irregularities in neuroanatomy such as swollen mitochondria, disrupted myelin sheaths, enlarged axons, and vacuolated Schwann cells have been exhibited by rats [16].

3.4. Human Studies: Role of Mitochondrial function in Mental Health

Mitochondrial Volume

Human fetal brain samples in areas with fluorosis have a significantly lower volume and density of mitochondria compared to those that have not been exposed [10]. A fluoride study on Chinese children illustrated how low-to-moderate water fluoride and urinary fluoride levels show an inverse association with mtDNA levels (a marker of mitochondrial dysfunction) [28]. A 1 mg/L increase in the water fluoride concentration was correlated to a 0.10-unit decrease in relative mtDNA levels. Furthermore, a 1 mg/L increase in urinary fluoride concentration was correlated with a 0.12-unit decrease in relative mtDNA levels. Interestingly, the effects of fluoride exposure had a more severe impact on male children than on female children [28].

Mitochondrial Swelling, Autophagy, and Apoptosis

Mitochondrial swelling, autophagy, and apoptosis because of fluoride exposure have all been noted in multiple studies [17] [28][50][51]. Human neuroblastoma SH-SY5Y cells that have been chronically treated with fluoride have shown altered morphology, including elongation of the mitochondria, swelling, and cristae disorders observed via transmission electron microscopy. These significant structural changes indicate that fluoride exposure could lead to neurotoxicity [11].

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