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REVIEW ARTICLE

Putative mechanisms of genotoxicity induced by fluoride: a comprehensive review

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Abstract Genotoxicity is the ability of an agent to produce damage on the DNA molecule. Considering the strong evidence for a relationship between genetic damage and carcinogenesis, to elucidate the putative mechanisms of genotoxicity induced by fluoride are important to measure the degree of risk involved to human populations. The purpose of this article is to provide a comprehensive review on genotoxicity induced by fluoride on the basis of its mechanisms of action. In the last 10 years, all published data showed some evidence related to genotoxicity, which is due to mitochondrial disruption, oxidative stress, and cell cycle disturbances. However, this is an area that still requires a lot of investigation since the published data are not sufficient for clarifying the genotoxicity induced by fluoride. Certainly, the new information will be added to those already established for regulatory purposes as a safe way to promote oral healthcare and prevent oral carcinogenesis.

Keywords Fluoride · Genotoxicity · In vitro studies · In vivo studies · DNA damage

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Introduction

Genotoxicity is the ability of an agent to produce damage on the DNA molecule. This pathobiological event has several biological implications because genetic damage is closely involved to several diseases including cancer. Herein, this is mandatory to better understand if and to what extent genotoxicity occurs in eukaryotic cells under different scenarios and paradigms. Such information will help to understand the pathways involved to this process in order to purpose strategies to avoid negative consequences. The scientific community has developed many genotoxicity assays able to detect DNA damage in eukaryotic cells from physical, chemical, or biological sources. Such methodologies detect a whole spectrum of genetic lesions such as single or double strand breaks, abasic sites, DNA adducts, mutations, and incomplete repair sites.

In the last decades, genotoxicity assays have also been applied in biomonitoring studies following the time course of diseases and to estimate the human health risk. These data have showed relevant information concerning levels of risk as well as the susceptibility status of human populations exposed to agents that have been proven to be genotoxic (Ribeiro 2012). To date, a variety of assays have been recognized when studying genotoxicity including those that evaluate DNA breakage, metaphase chromosomal aberrations, sister chromatid exchanges, and DNA repair system (Bolognesi et al. 2013).

It is an undeniable fact that fluoride prevents dental caries (Aoba and Fejerskov 2002). The trace element possesses many chemical properties being the most important to form ionized fluorides with several other elements (Chlubek et al. 2003). Nowadays, eukaryotic cells and tissues are continuously exposed to fluoride via food, drinking water, additives, toothpastes, or by professional administration (Shulman and

Wells 1997). This leads to high fluoride exposure, which induces a toxicological condition known as fluorosis. Fluorosis is very toxic to living organisms (World Health Organization 2006), and it causes severe damage in various tissues like bones, teeth, skeletal muscles, ligaments, gastrointestinal system, and erythrocytes (Goodarzi et al. 2016). Fluoride is recognized by international regulatory agencies as an important natural and industrial environmental pollutant (Whitford 1983).

Considering the strong evidence for a relationship between genetic damage and carcinogenesis (Ribeiro 2012), elucidation of mechanisms of genotoxicity induced by fluoride is important to measure the degree of risk involved as far as to mitigate potential risks to human populations. Thus, it is necessary to compile the scientific information in such a way that they can purpose strategies for new studies be capable of clarifying the doubts present within the field.

The purpose of this article is to provide a comprehensive review for elucidating the putative mechanisms of genotoxicity induced by fluoride.

Material and methods

A comprehensive literature search for studies on "DNA damage, genetic damage, genotoxicity and fluoride" was performed in the last 10 years. In brief, a search of PubMed, MEDLINE, Embase, and Google Scholar for a variety of articles (all publications until January 2017) was carried out. Case reports and papers did not written in English language were excluded from the review. All papers were identified and included in this review.

Results

In vitro studies

After reviewing the scientific literature, there are some studies investigating the genotoxic potential of fluoride so far. In vitro studies pointed out mitochondrial disruption, oxidative stress, and cell cycle disturbances as indicative end-points of genetic damage induced by fluoride exposure. For example, some authors have demonstrated that fluoride at lower concentrations induced oxidative stress leading to apoptosis on human lymphocytes in vitro (Jothiramajayam et al. 2014). The same was observed in rat embryonic hepatocytes (Wang et al. 2004). The results also suggested that fluoride at low concentrations may affect cell cycle progression. Particularly, such findings confirm biological mechanisms involved to fluoride-induced apoptosis (Jothiramajayam et al. 2014). By comparison, others have yet mentioned that fluoride exposure generates reactive oxygen species (ROS) by SIRT1/autophagy induction through c-Jun N-terminal kinase (JNK) signaling in ameloblasts affection enamel synthesis (Suzuki et al. 2015). Moreover, cytochrome c release, up-regulation of UCP2, attenuation of ATP synthesis, and H2AX phosphorylation (γH2AX), which are current biomarkers for DNA damaging, were detected (Suzuki et al. 2015). Odontoblast-like cells incubated with fluoride promoted caspase-3 activation and subsequent DNA fragmentation (Karube et al. 2009). The addition of fluoride-induced cell death was triggered by apoptosis in this cell line (Karube et al. 2009). Catalase treatment significantly inhibited cell death induced by fluoride (Nguyen Ngoc et al. 2012).

When cell cycle regulatory mechanisms were deeply investigated, interesting findings were reported. Fluoride treatment greater than 1 mM reduced viability and DNA synthesis as well as induced cell cycle arrest in the G(2)/M phase on mouse embryonic stem cells (Nguyen Ngoc et al. 2012). An increase in the proportion of cells in S phase was observed in response to the treatment of 40 and 80 mg/l of fluoride. NF-kappaB gene expression was also enhanced by fluoride treatment in a dose-dependent manner. The results indicated that fluoride could induce S phase cell cycle arrest, up-regulation of NF-kappaB, and subsequent DNA damage in primary rat hippocampal neurons (Zhang et al. 2008). Nevertheless, mouse lymphoma cells did not present any evidence of DNA breakage after exposure to fluoride in vitro (Ribeiro et al. 2006). Chinese hamster ovary cells were exposed in culture for 1 h at 37 °C to fluoride did not show genetic damage in increasing concentrations as well (Ribeiro et al. 2007). The same was observed when DNA repair system was investigated after fluoride exposure (Ribeiro et al. 2007). The increase of DNA damage was induced following treatment with methylmethanesulfonate or H_2O_2, but the fluoride did not alter the genotoxicity induced by these experimental exposures (Ribeiro et al. 2007). The data indicate that fluoride did not interfere with DNA repair system, by means of alkylation-induced genotoxicity or oxidative DNA damage (Ribeiro et al. 2007).

In vivo studies

Studies focusing on possible in vivo genotoxic effects of fluoride and related compounds have reported a probable link to oxidative stress and mitochondrial damage. Such events are able to induce genetic damage as a result of DNA fragmentation. These pathobiological mechanisms are summarized in Fig. 1.

Drosophila melanogaster exposed to different concentrations of fluoride showed a significant increase in HSP70 expression (Dutta et al. 2017). Genotoxicity was positive in this setting (Dutta et al. 2017). In addition, activity of AChE, oxidative stress marker enzymes from phase I and phase II

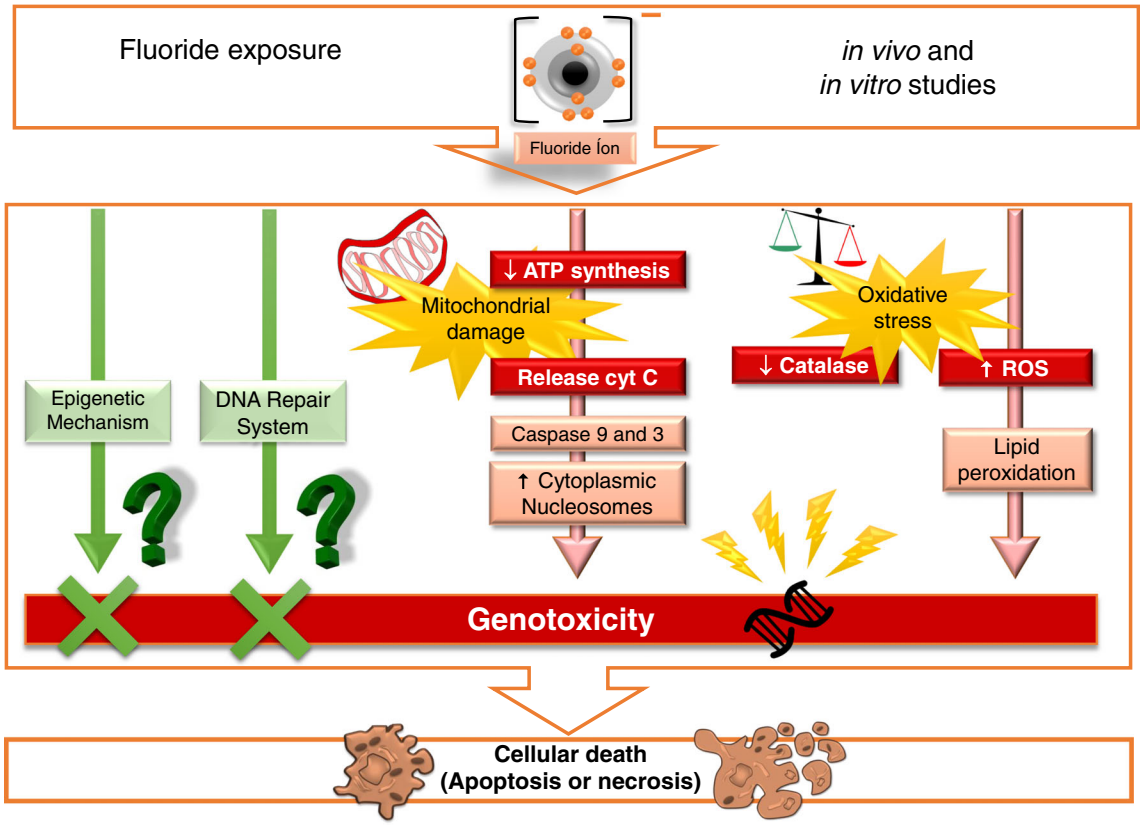

Fig. 1 Putative mechanisms induced by fluoride-based in vitro and in vivo studies

detoxifying enzymes, was inhibited in the larvae exposed to fluoride (Dutta et al. 2017).

For bone marrow cells, fluoride increased the frequency of micronucleus in polychromatic erythrocytes and induced structural chromosome aberrations (JM Sinha et al. 2013). Treatment of mice with sodium fluoride for 30 days increased the number of cell death and induced chromosomal aberrations in bone narrow cells (Podder et al. 2008, 2011a; 2011b). However, other authors did not show any evidence of genotoxicity following fluoride exposure in rat blood cells (Ribeiro et al. 2004). The expression of caspase-12 was increased in a dose-dependent manner after fluoride exposure. High concentrations of fluoride induced osteoblast apoptosis in vivo (Liu et al. 2015). It seems that fluoride exposure in blood cells is associated with increased oxidative stress in vivo (Flora et al. 2012). Moreover, fluoride promotes a higher population of annexin-V positive cells (Podder et al. 2011a).

Spleen cells did not show genetic damage in male mice exposed to fluoride (Podder et al. 2010a, b; JM Sinha et al. 2013). Conversely, administration of fluoride in mice decreased organo-somatic index accompanied by a decline in the white pulp content in this organ (Podder et al. 2010a, b). Sodium fluoride also induced apoptosis mediated by retoplasmic reticulum stress in the spleen of mice (Deng et al. 2016). This process was activated by up-regulation of caspase 12 (Deng et al. 2016). Growth arrest and DNA damage were also noticed in this study (Deng et al. 2016). Ultrastructural changes and genetic damage were noticed in thymus lymphocytes after exposure to fluoride (Wang et al. 2010). Molecular analysis showed that excessive fluoride ingestion significantly up-regulated the expression levels of caspase-3 and caspase-9 (Wang et al. 2010). Cell cycle arrest as a result of inhibition of DNA synthesis or perturbation of synthesis of cyclin was noticed to mice exposed to fluoride (Podder et al. 2010a, b).

The liver is the main metabolic organ of the whole organism. Therefore, it is very important to investigate it when studying the biological behavior of xenobiotics. Liver cells showed positive genotoxicity in murine liver exposed to fluoride (He and Chen 2006; Thangapandiyan and Miltonprabu 2013). However, others have evidenced that no genotoxicity is induced by fluoride at acute or subcronic treatment (Ribeiro et al. 2004; Leite Ade et al. 2007; Buzalaf et al. 2006). Histopathological lesions such as vacuolar degeneration, micronecrotic foci in the hepatocytes, and hepatocellular hypertrophy were evident in the mice exposed to fluoride, while sinusoidal dilation with enlarged central vein surrounded by deep-blue erythrocytes was preponderant when treated fluoride for a period of 90 days (Chattopadhyay et al. 2011). This findings was correlated to biochemical changes as for example reduced glutathione level (GSH), glutathione-s-transferase

(GST) activity, malondialdehyde (MDA) production, and heat shock protein 70 (Hsp 70) expression (Chattopadhyay et al. 2011). The same was detected by others (JM Sinha et al. 2013). The reactive content of reactive oxygen species increased significantly, whereas SOD and GSH-Px activities, as well as total antioxidant activity, decreased significantly after fluoride exposure (Das et al. 2008; JM Sinha et al. 2013; Zhou et al. 2015; Thangapandiyan and Miltonprabu 2013). Nitric oxide and malondialdehyde levels increased in liver cells after 70 days of fluoride treatment (Das et al. 2008; JM Sinha et al. 2013; Thangapandiyan and Miltonprabu 2013; Zhou et al. 2015). Fluoride also induced oxidative stress in fish liver cells (Mukhopadhyay and Chattopadhyay 2014).

Song et al. (2015) have detected apoptosis induced by fluoride in hepatocytes, especially at higher doses. Higher caspase-3 and caspase-9 expressions were evidenced in liver cells with increasing fluoride concentrations (Song et al. 2015). An earlier study conducted by Campos-Pereira et al. (2017) has demonstrated genotoxic potential of fluoride in rat hepatocytes but did not confirm mitochondrial damage or even the occurrence of apoptosis induced by fluoride. Taken together, oxidative stress and apoptosis induced by fluoride were verified by the scientific literature and were associated with DNA fragmentation in rat hepatocytes (Flora et al. 2012; Campos-Pereira et al. 2017; Das et al. 2008; Song et al. 2015). Therefore, we assumed that genetic damage induced by fluoride is induced by oxidative stress and mitochondrial damage.

Expression of some antioxidants enzymes such as catalase, superoxide dismutase, and reduced glutathione contents were decreased, whereas lipid peroxidation product (malondialdehyde) was increased in rat cardiac tissue exposed to fluoride. These results were associated with histopatological lesions and DNA damage (Miltonprabu and Thangapandiyan 2015; Umarani et al. 2015). Apoptosis was also detected in cardiac tissue exposed to fluoride (Miltonprabu and Thangapandiyan 2015).

Fluoride exposure induced testicular apoptosis, as depicted by several biomarkers such as caspase-3 activation, chromatin condensation, and DNA fragmentation (Zhang et al. 2016). Further study revealed that fluoride exposure elicited significant elevations in the levels of cell surface death receptor Fas with a parallel increase in cytoplasmic cytochrome c, indicating the involvement of both extrinsic and intrinsic apoptotic pathways (Zhang et al. 2016).Fluoride increased serum levels of oxidative stress, markedly elevated testicular fluorine, and 8-OHdG expression levels as well as the rate of sperm aberration (Feng et al. 2015). Histopathological changes in testicular seminiferous tubule were also evident in rats treated with fluoride (Feng et al. 2015). To assess global molecular toxicity in testis of mice administrated with fluoride, microarray analysis was performed to identify the altered transcriptions. The results revealed that 763 differentially expressed genes were identified, including 330 up-regulated and 433 down-regulated genes, which were involved in spermatogenesis, apoptosis, DNA damage, DNA replication, and cell differentiation (Su et al. 2017). Interestingly, more apoptotic spermatogenic cells were observed in the fluoride group, and the spermatogonium was markedly increased in S phase and decreased in G2/M phase after fluoride administration (Su et al. 2017). Other authors have demonstrated that fluoride exposure could disrupt spermatogenesis and testicles in mice by influencing many signaling pathways and genes, which work on the immune signal transduction and cellular metabolism (Huo et al. 2016). Particularly, the high expression of the IL-17 signal pathway was a response to the invasion of the testicular immune system due to extracellular fluoride (Huo et al. 2016). The PI3-kinase/AKT, MAPKs, and the cytokines in TGF-β family were contributed to control the IL-17 pathway activation induced by fluoride (Huo et al. 2016).

Some authors have demonstrated that fluoride increased apoptosis and DNA damage in kidney cells. In addition, fluoride treatment increased the protein expression levels of cytochrome C and cleaved caspases 9, 8, and 3 (Song et al. 2014). These results indicated that fluoride induces apoptosis in the kidney of rats through caspase-mediated pathway (Song et al. 2014). Histopathological damage was found in kidney tissue as depicted by blood filled spaces, disintegration of tubular epithelium, and atrophy of glomeruli after fluoride treatment being correlated with reduced glutathione level (GSH), glutathione-s-transferase (GST) activity, malondialdehyde (MDA) production, and heat shock protein 70 (Hsp 70) expression (Chattopadhyay et al. 2011).

Sub-acute exposure to fluoride at a dose of 20 mg/kgb.w./day for 30 days also caused significant alteration in pro-oxidant/antioxidant status of brain tissue as depicted by perturbation of reduced glutathione content, increased lipid peroxidation, protein carbonylation, nitric oxide, and free hydroxyl radical production and decreased activities of antioxidant enzymes of fluoride intoxicated rats (Flora et al. 2012; Pal and Sarkar 2014; Sarkar et al. 2014). DNA and RNA contents significantly decreased in cerebrum, cerebellum, and medulla after fluoride exposure (Sarkar et al. 2014). The same findings were observed by others using fish experimental model (Mukhopadhyay et al. 2015a, b). By contrast, primary DNA damage was not confirmed in brain cells exposed to fluoride (Ribeiro et al. 2004).

Conclusion

In this review, we have highlighted recent advances on genotoxicity induced by fluoride either in vitro or in vivo. All published data show some evidence related to genotoxicity, which is due to mitochondrial damage and oxidative stress (Fig. 1). Such events culminates in cellular death by activating pro-apoptotic caspases (caspases 3 and 9 and

others) or necrosis. However, further studies are welcomed including the use of other genotoxicity assays with different end-points, such as point mutations, chromosomal breakage as well as disruption of genetic apparatus in order to detect if fluoride is able to induce DNA mutations in several tissues and organs. Moreover, to study the interference of fluoride on DNA repair system or epigenetic mechanisms is fundamental for elucidating other possible mechanisms of genotoxicity induced by fluoride. Therefore, this is an area that still requires a lot of investigation since the published data is not sufficient for establishing the genotoxicity induced by fluoride with accuracy. Certainly, the new information will be added to those already established for regulatory purposes as a safe way to promote oral healthcare and prevent oral carcinogenesis.

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