Chemico-Biological Interactions 188 (2010) 319–333

Contents lists available at ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint

Mini-review

Molecular mechanisms of fluoride toxicity

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ARTICLE INFO

Article history:
Available online 3 August 2010

Keywords:
Fluoride toxicity
Oxidative stress
Gene regulation
Signal transduction
Fluorosis
Drinking water

ABSTRACT

Halfway through the twentieth century, fluoride piqued the interest of toxicologists due to its deleterious effects at high concentrations in human populations suffering from fluorosis and in *in vivo* experimental models. Until the 1990s, the toxicity of fluoride was largely ignored due to its "good reputation" for preventing caries via topical application and in dental toothpastes. However, in the last decade, interest in its undesirable effects has resurfaced due to the awareness that this element interacts with cellular systems even at low doses. In recent years, several investigations demonstrated that fluoride can induce oxidative stress and modulate intracellular redox homeostasis, lipid peroxidation and protein carbonyl content, as well as alter gene expression and cause apoptosis. Genes modulated by fluoride include those related to the stress response, metabolic enzymes, the cell cycle, cell–cell communications and signal transduction.

The primary purpose of this review is to examine recent findings from our group and others that focus on the molecular mechanisms of the action of inorganic fluoride in several cellular processes with respect to potential physiological and toxicological implications. This review presents an overview of the current research on the molecular aspects of fluoride exposure with emphasis on biological targets and their possible mechanisms of involvement in fluoride cytotoxicity. The goal of this review is to enhance understanding of the mechanisms by which fluoride affects cells, with an emphasis on tissue-specific events in humans.

Contents

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doi:10.1016/j.cbi.2010.07.011

1. Introduction

The fluoride ion is derived from the element fluorine, a gas that never occurs in a free state in nature. Fluoride is abundant in the environment and exists only in combination with other elements as fluoride compounds, which are constituents of minerals in rocks and soil. Therefore, fluoride is commonly associated with volcanic activity.

Sources of fluoride include natural fluoride in foodstuffs and water, i.e., fluoridated water (usually at 1.0 mg/l), fluoride supplements (such as fluoride tablets), fluoride dentifrices (containing on average 1000 mg/kg), and professionally applied fluoride gel (containing on average 5000 mg/kg). The main source of fluoride for humans is the intake of groundwater contaminated by geological sources (maximum concentrations reaching 30–50 mg/l). The level of fluoride contamination is dependent on the nature of the rocks and the occurrence of fluoride-bearing minerals in groundwater. Fluoride concentrations in water are limited by fluorite solubility, so that in the absence of dissolved calcium, higher fluoride solubility should be expected in the groundwater of areas where fluoride-bearing minerals are common and vice versa [1].

Excessive fluoride intake over a long period of time may result in a serious public health problem called fluorosis, which is characterized by dental mottling and skeletal manifestations such as crippling deformities, osteoporosis, and osteosclerosis. Endemic fluorosis is now known to be global in scope, occurring on all continents and affecting many millions of people [2].

In some regions, artificial fluorides used to fluoridate community water supplies (mostly at around 1 mg/l) include silicofluoride compounds (sodium silicofluoride and hydrofluosilicic acid) and sodium fluoride (NaF). At neutral pH, silicofluoride is dissociated to silic acid, fluoride ion, and hydrogen fluoride (HF) [3]. The primary benefit associated with fluoride supplementation is linked to the potential to reduce the risk of dental caries due to the cariostatic effects of fluoride. Even in the past, fluoride was considered an essential element. In actuality, there is a lack of consensus as to the role of fluoride in human nutrition and optimal development and growth [4].

Additional risks of increased fluoride exposure are known; the most significant are effects on bone cells (both osteoblasts and osteoclasts) that can lead to the development of skeletal fluorosis. It is now recognized that fluoride also affects cells from soft tissues, i.e., renal, endothelial, gonadal, and neurological cells [5].

The minimal risk level for daily oral fluoride uptake was determined to be 0.05 mg/kg/day [6], based on a non-observable adverse effect level (NOAEL) of 0.15 mg fluoride/kg/day for an increased fracture rate. Estimations of human lethal fluoride doses showed a wide range of values, from 16 to 64 mg/kg in adults and 3 to 16 mg/kg in children [6].

Organofluoride compounds (carbon–fluoride bond) are increasingly used. These compounds have a wide range of functions and can serve as agrochemicals, pharmaceuticals, refrigerants, pesticides, surfactants, fire extinguishing agents, fibers, membranes, ozone depletors, and insulating materials [7]. An estimated 20% of pharmaceuticals and 30–40% of agrochemicals are organofluorines [8]. However, environmental and health issues are still a problem for many organofluorines. Because of the strength of the carbon–fluoride bond, many synthetic fluorocarbons and fluorocarbon-based compounds are persistent global contaminants and may be harming the health of wildlife [7]. Their effects on human health are unknown. However, the toxicity of fluorinated organic chemicals is usually related to their molecular characteristics rather than to the fluoride ions that are metabolically displaced.

The present review is focused on the molecular effects of inorganic fluoride with respect to potential physiological and toxicological implications. It addresses the current understanding of the signal transduction pathways and mechanisms underlying the sensitivity of various organs and tissues to fluoride. This review provides information on the cellular and molecular aspects of the interactions between fluoride and cells, with an emphasis on tissue-specific events in humans.

2. Uptake and accumulation

Fluoride is very electronegative, which means that it has a strong tendency to acquire a negative charge and forms fluoride ions in solution. In aqueous solutions of fluoride in acidic conditions such as those of the stomach, fluoride is converted into HF, and up to about 40% of ingested fluoride is absorbed from the stomach as HF [9].

Fluoride transport through biological membranes occurs primarily through the non-ionic diffusion of HF. Classic studies with artificial lipid bilayers and pH electrodes indicated that HF is a highly permeant solute with a permeability coefficient similar to that of water. The small neutral molecule of HF seems to penetrate cell membranes much faster than the dissociated fluoride ion, resulting in a more pronounced intracellular intake [9]. Membrane permeability to HF is five to seven orders of magnitude above that of fluoride [10]. Recent studies showed that approximately 45% of ingested fluoride is absorbed from the intestine, and that fluoride absorption from the intestine is less sensitive to pH and may occur via a carrier-mediated process (i.e., facilitated diffusion) [11]. It is not known whether such carrier proteins are also present in the membranes of other cells.

In addition, fluoride permeability via anion channels has been demonstrated in airway epithelial cells [12], but Gofa and Davidson [13] suggest that fluoride potentiates the activity of potassium-selective ion channels in osteoblastic cells. The activity of potassium and calcium channels may mediate many of the early events in fluoride-induced cell activation. Apparently, there are several pH gradient-dependent, carrier-mediated mechanisms for fluoride transport; one may involve fluoride uptake in the form of HF by diffusion; in other, fluoride appears to cross membrane by a F^-–H^+ cotransporter or F^-–OH^- exchangers in the presence of an inward-directed proton gradient cells [10]; however, further studies are needed to clarify this subject.

Relative to the amount of fluoride ingested, high concentrations of cations that form insoluble complexes with fluoride (e.g., calcium, magnesium and aluminum) can markedly decrease