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Fluoride and Bronchial Smooth Muscle

Fedoua Gandia[1], Sonia Rouatbi[1],
Badreddine Sriha[2] and Zouhair Tabka[1]
[1]Laboratory of Physiology and Functional Explorations,
Faculty of Medicine Sousse, University of Sousse,
[2]Laboratory of Pathological Anatomy and Cytology,
Faculty of Medicine Sousse, University of Sousse,
Tunisia

1. Introduction

Fluoride is an inhibitor of enolase, an enzyme in glycolysis leading to phosphoenolpyruvate (Mayes, 1987). Inhibition of this enzyme would be expected to reduce glycolytic ATP production and impair smooth muscle contraction. It has also been reported that fluoride has contractile effect on vascular and airway smooth muscle mediated by the activation of guanine nucleotide binding proteins (G proteins) (Himpens et al., 1991; Kawase & Van Breemen, 1992; Leurs et al., 1991).

Fluoride (NaF) may thus induce either contraction or relaxation of smooth muscle depending on the particular conditions. NaF is less potent than aluminium fluoride (Al F^-_4) in the activation of G proteins, Al F^-_4 mimics the action of GTP at micro molar concentrations by inducing dissociation of the α subunit of G protein followed by the calcium channel modulation (Stadel & Crooke, 1988).

A close relationship between fluoride exposure and asthmatic symptoms was confirmed by several studies (Taiwo et al., 2006; Viragh et al., 2006; Fritchi et al., 2003; Soyseth et al., 1994) but little is know about its potential bronchorelaxant effect. In this chapter we will explore the effect of fluoride on respiratory status, its mechanism of action, its toxicity and factors that could influence its effects.

2. Fluoride intake

Fluoride is the ionic form of fluorine, a halogen and the most electronegative of the elements of the periodic table. It's a natural component of the biosphere and the 13th most abundant element in the crust of the earth.

Sources of fluoride include natural fluoride in food stuffs and water, i.e., fluoridated water (usually at 1.0 mg/l), fluoride supplements (such as fluoride tablets), fluoride dentifrices (containing on average 100 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 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 (Barbier et al., 2010).

Fluorides accumulate in the body lead to numerous metabolic disorders even at a low concentration but with long time exposure. Chronic long-term exposure to high levels of fluoride leads to fluorosis, a serious health problem in many parts of the world, where drinking water contains more than 1-1.5 ppm of fluoride (World Health Organization, 1984). However, the exposure of humans to fluorine is also connected with its presence in the air and food.

3. Fluoride metabolism

Fluoride is very electronegative, which means that it has a strong tendency to acquire a negative charge forms fluoride ions in solution. In aqueous solutions of fluoride in acidic conditions such as those of the stomach, fluoride is converted into HF (weak acid with pK_a of 3.4) (Whitford, 1994). There is a considerable body of evidence showing that several of the transmembrane migration of the ion occurs in the form of HF in response to differences in the acidity of adjacent body fluid compartments (Whitford, 1996).

Most commonly, fluoride is absorbed and enters the body fluids by way of the lungs or the gastrointestinal tract. In the absence of high certain cations, such as calcium and aluminium, that form insoluble compounds with fluoride, about 80-90% of the ingested amount is absorbed from gastrointestinal tract (Whitford, 1994; Whitford, 1996). Most of the fluoride that escapes absorption from the stomach will be absorbed from the proximal small intestine. Roughly 50% of an absorbed amount will be excreted in the urine during the following 24h while most of the remainder will be associated with calcified tissue. 99% of the fluoride in the body is associated with calcified tissues.

There are two general forms of fluoride in human plasma. One fraction is called ionic fluoride (also called inorganic or free fluoride). This form of fluoride is the one of significance in dentistry, medicine and public health. It is detectable in plasma by the fluoride electrode and is not bound to plasma proteins. The other fraction is nonionic fluoride (also called organic of bound fluoride). Together, the ionic and nonionic fractions constitute what is commonly called 'total' plasma fluoride (whitford, 1994, 1996). The concentration of fluoride in plasma varies according to the level of intake and several physiological factors (whitford, 1996). In general, the numerical value of the fasting plasma concentration of healthy adults is equal to that in the drinking water. Then, the fasting plasma concentration of a person whose water contains 1.0ppm would be about 1.0 μmol/L. If the water contained 2.0ppm, the plasma concentration would be about 2.0μmol/L. The variations of these values would be due largely to individual differences in the rates of removal of fluoride by the kidneys and skeleton.

4. Fluoride and asthma

The relationship between exposure to fluoride and bronchial responsiveness was investigated since 1936; scientists have observed that workers exposed to airborne fluorides suffer from an elevated rate of respiratory disorders.

(Taiwo et al., 2006) in a study conducted to evaluate the respiratory risks from fluoride inhalation, showed hat there was a significant statistical relationship between the incidence of asthma and the mean gaseous fluoride exposure in the study population whereas the relationship between asthma incidence and the other contaminants was less significant.

In a 7 years study conducted by (Viragh et al., 2006) to evaluate the respiratory effects of fluorine compounds on exposed workers in a small-scale enamel enterprise found, that fluorine exposure may be responsible for the high incidence of chronic irritative respiratory diseases, especially for chronic bronchitis in exposed workers.

(Fritchi et al., 2003) had demonstrated that the relevant causative agents for respiratory symptoms in aluminum smelters are fluoride and inspirable dust.

A close relationship between the levels of fluoride exposure and work-related asthmatic symptoms has been observed by many studies (Kongerud et al., 1994; Soyseth et al., 1994; Soyseth & Kongerud, 1992; Kongerud, 1992; Tatsumi et al., 1991).The risk to respiratory function from fluoride exposure is independent of the risk from smoking, but the combination of fluoride exposure and smoking presents a risk greater than either factor by itself. In fact in a study conducted by (Kongerud & Samuelsen, 1991), they conclude that current total fluoride exposure and smoking are the major risk factors for development of dyspnea and wheezing in aluminium potroom workers.

Animal experiments studies converge of respiratory damage caused by fluoride, inflammation, emphysema and pulmonary cellular alterations (Mullenix, 2005; Yamamoto et al., 2001).

4.1 Fluoride effects on bronchial smooth muscle

The contractile effect of fluoride (NaF) was well documented. Previous studies confirms that NaF contracts several muscles such as, sheep pulmonary arterial rings (Uzun et al., 2002), rat intestinal smooth muscle (Murthy et al., 1992) isolated rat aorta and mesenteric artery (Hattori et al., 2000), and guinea-pig airway smooth muscle (Leurs et al., 1991). Several mechanisms have been proposed to explain NaF-induced contraction. In these studies, NaF was used as source of fluoride (F^-), and the effect obtained were owing to fluoride not to Na.

Flouride is a well-known G-protein activator. Activation of heterotrimetric GTP-binding proteins by F requires trace amounts of aluminum (Al^{3+}) or beryllium (Be^{2+}) ions (Li, 2003). F^- is a potent stimulator of G_s, G_i, G_p and transducin . NaF-induced vascular contractions have been proposed to be attributable to fluoride complexing with aluminum, which can come from contamination of glassware, to form fluoroaluminates (Al^{F4-}), which are activators of G proteins (Hattori et al., 2000). AlF $^{4-}$ has a structure similar to phosphate (PO_4 $^{3-}$) and is able to interact with the guanosine 5` -diphosphate (GDP) situated on the α-subunit of the G-proteins, resulting in activation by mimicking GTP at its binding site (Bigay et al., 1985; Wang et al., 2001).

Furthermore, it has been reported that NaF has a contractile effect on airway smooth muscle mediated by both G protein-dependent and -independent pathways (Murthy & Makhlouf,

1994). Activation of G proteins by fluoride in smooth muscle cells can initiate a series of events, such as Ca^{2+} mobilization and phospholipase C (PLC) and protein kinase C (PKC) activation (Weber et al., 1996). In vascular endothelium, NaF activates a pertussis toxin-insensitive GTP-binding protein, which leads to increases in phosphoinositide hydrolysis, Ca^{2+} mobilization from intracellular stores, arachidonate release, and prostacyclin synthesis (Garcia et al., 1991).

Fluoride has the capacity to both contract and dilate smooth muscle. These effects are closely related to the dose. NaF has been reported by (Stadel & Crooke, 1988; Cushing et al, 1990) to stimulate adenylate cyclase activity on smooth muscles and induced No synthesis which would relax bronchi. The better known bronchodilator mechanism of NaF is induced by inhibition of glycolytic enzyme, enolase, which converts 2-phosphoglycerate to phosphoenolpyruvate according to (Zhao W & Guenard H, 1997). The inhibition of glycolysis induced by NaF is illustrated by the sharp decrease in lactate production in its presence (Zhao W et al, 2002). Inhibition of this enzyme would be expected to reduce glycolytic ATP production and impair smooth muscle contraction.

This bronchodilator effect of NaF is thus far poorly documented. Inconsequence, its use as therapeutic agent for asthma disease is very limited despite its bronchodilator effect demonstrated at well defined dose both in vitro and in vivo by recent and previous studies (Gandia F et al, 2010; Rouatbi S et al, 2010; Zhao W & Guenard H, 1997; Zhao et al 2002).

4.2 Effect of fluoride dose on bronchial smooth muscle

Fluoride at a micromole level is considered an effective anabolic agent because it promotes cell proliferation whereas millimolar concentrations inhibit several enzymes, including phosphatases, both in vivo and in vitro (Barbier et al, 2010).

At toxicological concentrations, i.e. in the mM range, many effects of fluoride on respiratory status have been described which depend on three factors, the fluoride concentration, the length of exposure and the associated cation. For example, 5 mM NaF has a modest effect on the IL-6 and IL-8 secretion by of a human epithelial cell 24h after addition, which was strongly enhanced by addition of Al^{3+} (Refsnes et al, 1999). Another study showed that 0.5 mM NaF enhances IL-1 beta mRNA expression from lung lavage cells (Hirano et al, 1999). NaF, between 0.5 and 10 mM, induce a concentration-dependent contraction in bovine bronchial smooth muscle (Zhao et al, 1997). NaF at 0.5mM induce a bronchorelaxation effect by decrease of bronchial resistances in rats precontracted by acetylmethylcholine analogs and serum concentration of fluoride was within the usual range in blood samples obtained from rats receiving this drug (Gandia et al., 2010). Inhibitory effect of NaF on glycolytic enzyme enolase can be observed in the 10μM range (Curran et al, 1994) on bacteria, which could be of interest in certain lung diseases.

5. Fluoride toxicity

Fluoride toxicity is characterized by a variety of signs and symptoms poisoning most commonly occurs following ingestion (accidental or intentional) of fluoride-containing products. Symptom onset usually occurs within minutes of exposure. Fluoride has several

mechanisms of toxicity. Ingested fluoride initially acts locally on the intestinal mucosa. It can form hydrofluoric acid in the stomach, which leads to G1 irritation or corrosive effects. Following ingestion, the G1 tract is the earliest and most commonly affected organ system.

Once absorbed, fluoride binds calcium ions and may lead to hypocalcaemia. Fluoride has direct cytotoxic effects and interferes with a number of enzyme systems; it disrupts oxidative phosphorylation, glycolysis, coagulation, and neurotransmission (by binding calcium). Fluoride inhibits Na^+/K^+-ATPase, which may be partly responsible for hyper salivation, vomiting, and diarrhea (cholinergic signs). Seizures may result from both hypomagnesaemia and hypocalcaemia (Barbier et al, 2010; Whitford, 1996).

Severe fluoride toxicity will result in multiorgan failure. Central vasomotor depression as well as direct cardio toxicity also may occur. Death usually results from respiratory paralysis, dysrhythmia or cardiac failure.

The minimal risk level for daily oral fluoride uptake was determinates to be 0.05 mg/kg/day (Whitford, 1996), based on 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 kg in children (Withford, 1996).

6. Conclusion

Fluorides are known to exert a variety of effects in different cell types. Fluoride has the capacity to both contract and dilate smooth muscle. The mechanisms of the relaxant and contractile effects appear to be divers. The former being related to the inhibition of glycolysis and the latter to the calcium channel modulation. While the relationship of fluoride and asthmatic symptoms was widely studied, little is know about its potential therapeutic uses in asthma. The effects induced by fluoride are closely related to dose and concentration. However, it's important to highlight that fluoride is a strong, hard anion and a cumulative toxic agent. Then, serum fluoride determination should be carefully monitored. Further toxicological investigations are needed to conclusively determine the indications for fluoride use and dose.

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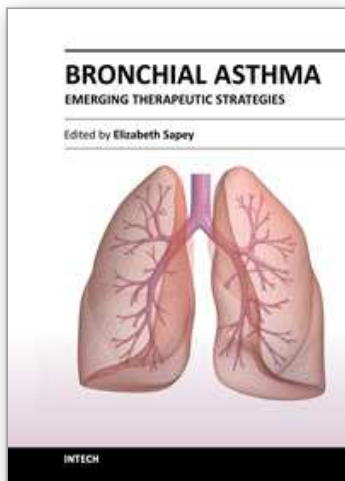
Bronchial Asthma - Emerging Therapeutic Strategies

Edited by Dr. Elizabeth Sapey

Asthma remains a serious health concern for millions of people globally. Despite continuing research interest, there have been few advancements that impact clinically on patient care, potentially because asthma has been treated as a homogeneous entity, rather than the heterogeneous condition it is. This book introduces cutting-edge research, which targets specific phenotypes of asthma, highlighting the differences that are present within this disease, and the varying approaches that are utilized to understand it.

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