Fluoride Vol. 35 No. 2 73-77 2002 Editorial Review 73

INTERACTIONS BETWEEN FLUORINE AND ALUMINUM

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Interactions between fluorine (as F^-) and aluminum (as Al^{3+}) have recently attracted much attention following reports of their possible involvement in Alzheimer's disease (AD). An inverse correlation has been demonstrated between the incidence and severity of AD and the level of fluorine in drinking water.[1-4] Aluminum has long since been implicated in the etiopathology of AD, and neurotoxicity studies have confirmed that it inhibits acetylcholine transferase and dihydropteridine reductase activities, depleting the central nervous system (CNS) of tyrosine and several neurotransmitters. By binding with nucleic acids, aluminum interferes with intracellular protein metabolism.[5-7]

Cunat *et al* have studied absorption *in situ* of aluminum compounds in perfused rat intestine.[8] Their findings demonstrate that organic compounds are more potent in modifying aluminum uptake than inorganic ones. The studies of Allain *et al*[9] as well as those of Spencer *et al*[10] have shown that the simultaneous administration of fluorine and aluminum in drinking water increased plasma concentrations of aluminum in rats. The same authors have reported that fluoride enhances the uptake of aluminum, whereas aluminum suppresses the uptake of fluoride. This effect seems to depend on the high affinity of aluminum to fluoride and the formation of complexes in the gastrointestinal tract associated with the breakdown of polymer forms and rapid uptake of aluminum by cells of the intestinal mucosa.[11]

Glynn *et al* in their studies on the uptake of aluminum in rats and the effect of fluoride, citrate, or silicate on this process have confirmed the formation of soluble complexes with citrate and fluoride, such as aluminum citrate (97%) and aluminum fluoride (60%). However, changes in absorption of aluminum were observed with citrate only.[12]

Reports on interactions between fluorine and aluminum in the gastrointestinal system have prompted other researchers to focus on biotoxicity. Forbes and Agwani[13] in their epidemiological survey conducted in several regions of the province of Ontario found an association between the incidence of psychiatric disorders and low levels of fluoride and SiO_2 in drinking water, advancing the view that both SiO_2 and fluoride protect against the toxicity of aluminum. Gauthier *et al*[3] did a similar study in the province of Quebec searching for associations between chronic exposure to aluminum compounds (like AlF_3) in drinking water and the incidence of AD, but they

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were unable to confirm the hypothesis of Forbes and Agwani. Unfortunately, interpretation of these results is uncertain due to the fact that the uptake of aluminum and fluoride from drinking water could not be monitored.

A more precise insight into the interactions of fluorine and aluminum is afforded in animal studies with various doses of fluorine and aluminum administered separately or in combination. Varner *et al* exposed three groups of rats to AlF_3 at 0.5, 5, and 50 ppm Al^{3+} during 45 weeks and found the highest morbidity and mortality with the lowest concentration.[14] According to these authors, fluorine played a dominant role in the toxicity but its uptake was reduced in groups exposed to high concentrations of aluminum. Based on the anti-caries protective effect of fluorine reported in epidemiological studies, it can likewise be inferred that the amount of fluorine complexed with aluminum was insufficient to exert a protective action in the group receiving the lowest dose of AlF_3.

Another study by these researchers compared the influence on the rat central nervous system of AlF_3 at 0.5 ppm Al^{3+} and 2.1 ppm NaF (1 ppm F^-) in either case administered in drinking water during 52 weeks.[5] No differences were observed after accounting for the weight of the animals, although mortality was higher in the group exposed to AlF_3. The concentration of aluminum in the nervous system was higher in both groups as compared with controls. The aluminum content in kidneys was twice as high in the AlF_3 than in the NaF group, while hepatic concentrations were at a similar level. Disorders in the integrity of neurons and the cerebral vasculature, reduced density of neurons in the cerebral cortex of the left hemisphere, abnormalities in chromatin clustering and staining, pyknosis and vacuolization were much more frequent in the AlF_3 group.

The role of fluorine in aluminum neurotoxicity has been addressed by van der Voet *et al* using cultured cells of the hippocampus obtained from rat fetuses and exposed to NaF or AlF_3, either separately or in combination.[15] When AlF_3 was administered alone, the formation of connections between nerve fibers was abnormal. This effect was increased when AlF_3 was combined with NaF. Apparently, aluminum interferes with the metabolism of the cytoskeleton in the nerve cells and the effect is potentiated by fluorine. The simultaneous administration of both elements produced aggregates of hippocampal neurons.

A distinct, well recognized and important role of fluorine in metabolic processes relates to the mineralization of hard tissues and prevention of caries. It has been confirmed that aluminum suppresses the uptake of fluoride and by modifying the metabolism of phosphorus, calcium, magnesium and fluorine favors the development of osteomalacia and osteodystrophia.[11,16] Ahn *et al* have studied the influence of several doses of fluorine and aluminum in drinking water on the uptake and accumulation of these elements in

incisors, tibia and sternum of rabbits.[16] The results confirm the inhibitory properties of aluminum on fluorine uptake. Furthermore, exposure of rabbits to 50 ppm F during 10 weeks led to the accumulation of aluminum in bones. Examination of osteoblasts has shown that the F-Al complex enhances the transport of inorganic phosphorus (Pi) induced by fluoride, supporting the hypothesis that this complex interacts with protein G receptors involved in phosphorylation of tyrosine as a regulatory event during the transport of Pi in osteoblasts.[17]

The influence of aluminum and fluorine administered separately or together on the function of ovaries and uterus of mice has been studied by Chinoy and Patel.[18] These authors found that administration of 10 mg NaF/kg-bw and 200 mg $AlCl_3$/kg-bw during 30 days led to a marked reduction in protein content of the ovaries and uterus, estradiol concentrations in serum, as well as activities of 3β- and 17β-hydroxysteroid dehydrogenase in ovaries and phosphorylase in uterus. In effect, a marked increase in the uterine glycogen content was observed. Additionally, cholesterol levels were elevated in the ovaries and serum. Simultaneous exposure of the animals to NaF and $AlCl_3$ was associated with an increased toxic effect on gonadal steroidogenesis, uterine metabolism of carbohydrates, and hypercholesterolemia, as compared with each compound administered separately.

In this issue of *Fluoride*, Gago, Marcos, and Alvarez[19] examine aluminum speciation in aqueous extracts of forest soils affected by fluoride emissions from an aluminum smelter. They found three forms of aluminum: acid-soluble, non-labile (organic monomeric), and labile (inorganic monomeric). In contrast to control samples, most labile aluminum in the vicinity of the factory was bound to fluoride, and the Al^{3+} activity was extremely low. Since the ion is considered as the most phytotoxic, the formation of Al-F complexes and reduction of Al^{3+} is of great beneficial value. The most abundant Al-F complexes were AlF^{2+} and AlF_2^{+}.

In studies on *Methanosarcina thermophila* by Miles *et al,*[20] aluminum fluoride in the form of AlF_3 or AlF_4^{-} was proposed to mimic the phosphoryl group in the catalytic transition state of acetate kinase, which catalyzes phosphoryl transfer of the ATP g-phosphate to acetate (cf. ref. 4). The experiments showed an increase in binding affinity of acetate kinase for MgADP in the presence of $AlCl_3$, NaF, and acetate. The transition state analog, MgADP-aluminum fluoride-acetate, formed an abortive complex in the active site of the enzyme.

Research results to date are equivocal as to the effects of fluorine and aluminum on the structure of tissues and organs, organ metabolism, and enzyme activities. Some authors have found a synergistic effect of both elements while others have contradicted these findings.

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