

HEALTH/BIOLOGICAL EFFECTS**Increased incidence of spina bifida occulta in fluorosis prone areas**

Spina bifida, a congenital deformity of the posterior wall of vertebrae of the spine, is a midline defect of skin, vertebral arches and neural tube, usually in the lumbosacral region. Its incidence is reported to be 0.2 to 0.4 per 1000 live births. Various hypotheses have been put forward as etiological factors for spina bifida including consumption of potato affected by blight and hardness of drinking water but these have not been proven. Two groups of 50 randomly chosen children were established. The study group consisted of children aged 5 to 12 years, weighing 15 to 30 kg, consuming fluoride-rich drinking water (4.5 and 8.5 ppm fluoride; WHO permissible limit is 1.5 ppm fluoride), and manifesting either clinical, dental and/or skeletal fluorosis. The control group consisted of age and weight-matched children, consuming less than or equal to 1.5 ppm fluoride in drinking water and not showing any evidence of fluoride toxicity. These children were evaluated for antenatal history, general clinical examination (especially for dimples, tufts of hair, haemangioma on skin throughout the length of spine), other congenital abnormalities, evidence of fluoride toxicity, biochemical estimation for fluoride levels in blood and serum and by skiagrams of the spine to examine for the presence of spina bifida occulta. A total of 22 (44%) of the 50 children in group A, the study group, and 6 (12%) of the 50 children in group B, the control group, revealed spina bifida occulta in the lumbosacral region.

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Keywords: Epidemiology, Fluorosis, Spinal bifida occulta.

Source: *Acta Paediatr Jpn* 1995 Aug;37(4):503-6.

Fluoride-induced ultrastructural changes in exocrine pancreas cells of rats: fluoride disrupts the export of zymogens from the rough endoplasmic reticulum

Influence of fluoride on exocrine pancreas cells was examined morphologically with traditional and prolonged osmium fixation techniques for electron microscopy in the enamel fluorosis model rats injected subcutaneously twice a day with 20 mg/kg body weight of sodium fluoride. Although the rough endoplasmic reticulum (rER) of exocrine pancreas cells in control rats was laminated and oriented parallel to the circumference of the nucleus, the rER of the cells in NaF-treated rats was dilated, disrupted the laminated arrangement, and changed to the globular-shape rER. Many intracisternal granules were formed in these globular-shape rER of the cells exposed to fluoride. Lots of autophagosomes were also seen in the exocrine cells with NaF treatment. The autophagosomes were limited with a double or multiple membranes, and contained cytoplasmic organelles and/or the intracisternal granules. The outer and inner leaflets of double membranes of the autophagosomes were usually separated

by a distinct electron-lucent area. In prolonged osmium fixation, the area between the double membranes of the autophagosome was filled with osmium reaction deposits. Many autophagosomes were encircled with the single or multiple osmiophilic layers. In some cases, the osmium positive saccules also surrounded the free surface of the globular-shape rER containing intracisternal granules. These findings indicate that fluoride disrupts the export of zymogens from the rER, resulting in formation of intracisternal granules and autophagosomes, and that the osmiophilic saccules participate in sequestration of cytoplasmic organelles in forming autophagosomes.

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Keywords: Fluoride, Pancreas, Rat study, Rough endoplasmic reticulum, Ultrastructural change.

Source: Arch Toxicol 2000 Feb;73(12):611-7.

Fluoride in drinking water and cancer mortality in Taiwan

The possibility that cancer risk is associated with naturally fluoridated water in Taiwan is examined. The 1982-1991 age-adjusted mortality rates for cancer for 10 municipalities whose water supplies contained the highest naturally occurring fluoride concentrations in Taiwan were compared to those rates for 10 matched municipalities with unfluoridated water. The two groups had similar urbanization levels and sociodemographic characteristics. Our study does not support the suggestion that fluoridation of water supplies is associated with an increase in cancer mortality in Taiwan.

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Keywords: Cancer, Epidemiology, Fluoride in water, Taiwan.

Source: Environ Res 2000 Mar;82(3):189-93.

Dental caries and fluorosis prevalence study in a nonfluoridated Brazilian community: trend analysis and toothpaste association

The main purpose of this study is to compare data from previous surveys to current prevalence rates of dental caries and dental fluorosis in eleven- and twelve-year-olds in a nonfluoridated Brazilian community (< 0.2 ppm F). This study also assesses the possible association between use of fluoride toothpaste and the prevalence of dental caries and dental fluorosis. The sample subjects are randomly selected schoolchildren who were examined with a dental probe and buccal mirror under natural light. The intraexaminer error was calculated, using Kappa statistics (K tau 0.85). The results showed that between 1991 and 1997 there was a 56.7 percent decrease in the prevalence of dental caries and an 80.1 percent increase in dental fluorosis. Children with dental fluorosis were 1.75 times more likely to be free of caries (OR = 1.75-CI:0.43, 6.68). Children

who started using fluoride toothpaste before the age of three were 4.43 times more likely to have dental fluorosis than those who started using it after the age of three (OR = 4.43-CI:0.51, 99.61). The results of the cross-sectional surveys conducted with schoolchildren in 1991, 1995, and 1997 suggest a continuing decrease in the prevalence of dental caries and an increase in the prevalence of dental fluorosis in this nonfluoridated Brazilian town.

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Keywords: Brazil, Dental caries, Dental fluorosis, Epidemiology, Toothpastes.

Source: ASDC J Dent Child 2000 Mar-Apr;67(2):132-5, 83.

In vitro effects of sodium fluoride and sodium dichromate on dynamic properties of human erythrocyte membrane

Sodium fluoride (NaF) and sodium dichromate ($\text{Na}_2\text{Cr}_2\text{O}_7$) are two different toxic compounds which are used as a dental caries prophylactic and as an oxidising agent in various industrial areas, respectively. However, accidental fluoride and chromate poisoning is not a rare occurrence, even death may result from cardiac or respiratory failure. In the present work, alterations produced by NaF, $\text{Na}_2\text{Cr}_2\text{O}_7$ and temperature changes in the molecular dynamics of the human erythrocyte membrane were studied, *in vitro*, by the spin-labeling ESR technique. Human intact erythrocyte cells spin labeled with 5- and 16-doxyl stearic acids (5-DSA and 16-DSA) and treated with 40 μM NaF and 5 μM $\text{Na}_2\text{Cr}_2\text{O}_7$ at 37 degrees C were used to quantify membrane fluidity. This was performed by measuring the changes in the order parameter (S), correlation time (τ) and phase transition temperature using recorded electron spin resonance (ESR) spectra. Experimental results show that 5 μM $\text{Na}_2\text{Cr}_2\text{O}_7$ and 40 μM NaF do not produce any significant effects on the order parameter of 5-DSA spin label while they cause appreciable changes in the correlation time of the same label. As for 16-DSA, while $\text{Na}_2\text{Cr}_2\text{O}_7$ does not produce any measurable effect on the order parameter of this label, NaF does to a certain extent. Although weak, the effects of both compounds on the correlation time of 16-DSA are found to be well above the experimental error limits. Change in temperature was observed to alter significantly S and τ parameters which show biphasic character in the temperature range of 5-50 degrees C. Activation energies of the hydrocarbon chains above and below transition temperatures were also determined for untreated and NaF or $\text{Na}_2\text{Cr}_2\text{O}_7$ treated erythrocyte cells and the effect of NaF and $\text{Na}_2\text{Cr}_2\text{O}_7$ on these energies and transition temperatures were discussed.

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Keywords: Red blood cells, Sodium fluoride.

Source: Biophys Chem 2000 Jan 17;83(2):111-20.

Some factors associated with the caries decline among Norwegian children and adolescents: age-specific and cohort analyses

The purpose of this study was to evaluate factors related to the caries decline in children between 1966 and 1983. The decline started in the late sixties for the 8- to 11- and the 17-year-olds, and after 1971 for the remaining age groups. Regression analyses confirmed a significantly different start of the decline. Fluorides in school-based programs, lozenges, and toothpaste, as well as education and sale of antibiotics were significantly ($p < \text{ or } = 0.01$) related to the caries decline in partial correlation analyses. Fluoride toothpaste was only significantly related to the decline in the last part of the period of observation. Supervised fluoride rinsing and brushing programs at school may explain most of the decline before 1971. The later decline may be related to all fluoride agents and to education. Use of fluorides and other preventive efforts aimed at pre-school children may have contributed to the continual decline in the number of fillings in the permanent teeth of the youngest cohorts.

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Keywords: Dental caries, Epidemiology, Fluoride treatments, Toothbrushing, Tooth-pastes.

Source: *Caries Res* 2000 Mar-Apr;34(2):109-16.

Water treatment with silicofluorides and lead toxicity

Toxic metals like lead, manganese, copper and cadmium damage neurons and deregulate neurotransmitters such as serotonin and dopamine (which are essential to normal impulse control and learning). Earlier studies show that – controlling for socio-economic and demographic factors – environmental pollution with lead is a highly significant risk factor in predicting higher rates of crime, attention deficit disorder or hyperactivity, and learning disabilities. Exposure and uptake of lead has been associated with industrial pollution, leaded paint and plumbing systems in old housing, lead residues in soil, dietary habits (such as shortages of calcium and iron), and demographic factors (like poverty, stress, and minority ethnicity).

We report here on an additional "risk co-factor" making lead and other toxic metals in the environment more dangerous to local residents: the use of silicofluorides as agents in water treatment. The two chemicals in question – fluosilicic acid and sodium silicofluoride – are toxins that, despite claims to the contrary, do not disassociate completely and change water chemistry when used under normal water treatment practices. As a result, water treatment with silicofluorides apparently functions to increase the cellular uptake of lead.

Data from lead screening of over 280,000 children in Massachusetts indicates that silicofluoride usage is associated with significant increases in average lead in children's blood as well as percentage of children with blood lead in

excess of 10 µg/dL. Consistent with the hypothesized role of silicofluorides as enhancing uptake of lead whatever the source of exposure, children are especially at risk for higher blood lead in those communities with more old housing or lead in excess of 15 ppb in the first draw water samples where silicofluorides are also in use. Preliminary findings from county-level data in Georgia confirm that silicofluoride usage is associated with higher levels of lead in children's blood. In both Massachusetts and Georgia, moreover, behaviours associated with lead neurotoxicity are more frequent in communities using silicofluorides than in comparable localities that do not use these chemicals. Because there has been insufficient animal or human testing of silicofluoride treated water, further study of the effect of silicofluorides is needed to clarify the extent to which these chemicals are risk co-factors for lead uptake and the hazardous effects it produces.

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Keywords: Fluoridation and blood-lead levels, Hydrofluosilicic acid, Sodium silicofluoride. Source: *Int J Environ Studies* 1999;56:435-49.

DIETARY FLUORIDE

Total fluoride intake and urinary excretion in 4-year-old Iranian children residing in low-fluoride areas

Knowledge of levels of fluoride ingestion and excretion is important in planning optimum fluoride therapy for young children. In previous literature, it has been assumed that only about one-third of ingested fluoride is excreted in young children. The aims of the present study were (a) to measure total fluoride intake, urinary fluoride excretion and fluoride balance, and (b) to investigate the effect of air temperature on fluoride intake and urinary fluoride excretion, in young children.

Children (4 years old) living in a city, a small town and rural areas of Fars province, Iran, where drinking water contained 0.30-0.39 mg F/L, were invited to participate. Selection of subjects was by random sampling of kindergartens or health centres. The children were surveyed twice, once in summer and once in winter. Diet was obtained by 3-day diaries with interview. Samples of most foods and drinks were analysed for fluoride content. Ingestion of fluoride from toothpaste was estimated for each child. Each child's urine was collected over 24 h and analysed for fluoride content.

Seventy-eight of the 116 volunteers completed all aspects of the study, which was conducted in 1995-6. For all children, the mean fluoride ingestion from diet was 0.390 (S.D. 0.122) mg/d or 0.028 (S.D. 0.008) mg/kg body weight per d. Fluoride ingestion from diet was higher in summer and higher in

rural areas. The mean ingestion of fluoride from all sources was 0.426 (S.D. 0.126) mg/d and the mean fluoride urinary excretion was 0.339 (S.D. 0.100) mg/d. The difference between ingestion and urinary excretion was +0.087 (SD 0.143) mg, equivalent to 80% excretion. Faecal excretion was not estimated. The results indicate fluoride retention at 4 years to be much lower than previously assumed.

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Keywords: Children, Fluoride excretion in urine, Fluoride in water, Food & dental, Iran.

Source: Br J Nutr 2000 Jan;83(1):15-25.

Fluoride content in Khat (*Catha edulis*) chewing leaves

Khat (qat) leaves are chewed for their psychostimulative effects; there is an unconfirmed suggestion that they contain a high concentration of fluoride (F). Khat samples from Yemen were suspended in deionized water, spun, and the supernatants exposed to a chelator that decomplexes F, which was assayed with an F⁻-electrode coupled to an ion analyser. F released into whole saliva after chewing khat for 15 min and from khat suspended in stimulated whole saliva for 1.5 h in vitro was measured also. Total F in dried khat leaves and their ash was assayed by the acid-hexamethyldisiloxane microdiffusion method. All methods demonstrated negligible amounts of F in or from khat leaves (<0.02 microg F/ml leached into water or saliva; 0.06 µF/mL in saliva after chewing; 0.93 microg total F/g in dried leaf, 2.07 microg total F/g in ash).

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Keywords: Fluoride in food.

Source: Arch Oral Biol 2000 Mar;45(3):253-5.

Urinary fluoride excretion by children 4-6 years old in a south Texas community

This study evaluated urinary fluoride excretion by school children 4-6 years old who were living in a south Texas rural community that had concentrations of fluoride in drinking water supplies generally around the optimal level. We took supervised collections of urine samples in the morning and afternoon at school, and parents of the participating students collected nocturnal samples. We recorded the beginning and end times of the three collection periods and then determined the urinary volume and urinary flow for each of the periods. We measured urinary fluoride concentrations and calculated the urinary excretion rate per hour. The children had breakfast and lunch provided at the school, where the drinking water contained 1.0-1.3 milligrams/liter (mg/L) fluoride. Fluoride concentrations in the tested household water supplies, from wells,

ranged from 0.1 to 3.2 mg/L fluoride. The children's average urinary fluoride concentrations found for the day were similar to those for the night, with means ranging from 1.26 mg/L to 1.42 mg/L. Average excretion was 36.4 μ /h in the morning, 45.6 μ /h in the afternoon, and 17.5 μ /h at night. The lower nocturnal excretion rates are easily explained by low urinary flow at night. Based on the 15 hours of urine collected, the extrapolated 24-hour fluoride excretion was 749 μ . In conjunction with similar studies, the data from this study will help in developing upper limits for urinary fluoride excretion that are appropriate for avoiding unsightly fluorosis while providing optimal protection against dental decay.

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Keywords: Circadian rhythm, Fluoride excretion in urine, Fluoride in water.

Source: Rev Panam Salud Publica 2000 Apr;7(4):242-8.

Weaning food and magadi associated with dental fluorosis in Northern Tanzania

A cross-sectional study of 143 children aged 10-14 years was carried out to identify factors associated with the severity of dental fluorosis in 2 areas (Moshi/Kibosho: n = 63/80) with fluoride (F) concentrations < 0.4 mg F/L in the drinking water. Dental fluorosis was recorded under field conditions using the Thylstrup and Fejerskov index (TFI). The score on tooth 21 was used to indicate the severity. The prevalence of dental fluorosis in Moshi at TFI score ≥ 1 was 60% and at TFI score ≥ 5 it was 10%. The corresponding values in Kibosho were 100% and 34%, respectively. Background variables pertained primarily to the child's first 6 years of life. In Moshi and Kibosho, 65% and 97% of children, respectively, used magadi, a fluoride-containing food tenderizer. In Moshi, the risk of having TFI score ≥ 2 was significantly higher among users of magadi (odds ratio (OR) = 5). Kiborou, a traditional homemade weaning food (porridge) cooked with magadi, was used only in Kibosho. Users of kiborou (36%) were at significantly higher risk (OR = 3) of developing fluorosis at severity TFI ≥ 4 than the users of lishe, another type of weaning food. All children in Moshi and 64% in Kibosho used lishe, which is cooked without magadi. Magadi and kiborou were significant risk indicators. Thus, it seems that the unexpectedly high prevalence of dental fluorosis and the observed differences in fluorosis prevalence and severity may be partly explained by F exposure from magadi.

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Keywords: Dental fluorosis, Fluoride in food.

Source: Acta Odontol Scand 2000 Feb;58(1):1-7.

ENVIRONMENTAL EFFECTS**The fluoride content of antlers as an indicator of fluoride exposure in red deer (*Cervus elaphus*): A historical biomonitoring study**

Bone fluoride concentrations were analyzed in 141 red deer antlers grown between the 17th/early 18th century and 1997, that originated from four study areas (Arnsberg, Bad Berleburg, Dammerwald, Schmidtheim) in the federal state of North Rhine-Westphalia, Germany. Fluoride concentrations in the specimens ranged between 27.7 and 1,392.1 mg F⁻/kg ash and varied significantly both between samples collected during different time-spans in the same area and between samples taken from different study areas over the same period. For antlers (n = 8) collected prior to 1860 in the study areas Arnsberg and Schmidtheim, values between 27.7 and 78.7 mg F⁻/kg ash were recorded. It is assumed that antler fluoride contents in this range are quite close to baseline levels for these regions, i.e., represent concentrations largely unaffected or only slightly influenced by fluoride from anthropogenic sources. With the onset and expansion of large-scale industrial activities, bone fluoride concentrations in the antler samples markedly increased over these baseline values, indicating fluoride deposition from industrial emissions into the red deer habitats. In the later 1980s and the 1990s, a pronounced decline in antler fluoride content was observed, which is attributed to the reduction of industrial fluoride discharges due to effective emission control programs. However, even the lowest fluoride values recorded for antlers grown in the 1990s (study area Schmidtheim, n = 10, range 158.5-367.3 mg F⁻/kg ash) clearly exceeded the concentrations found in the antlers collected prior to 1860, thereby indicating an additional fluoride burden from anthropogenic sources on the recent populations. The present study has corroborated the view that antlers are good indicators of fluoride exposure in deer. The fact that they grow during a seasonally fixed time-span and thus constitute relatively well "naturally standardized" samples and are often kept over long periods of time make antlers suitable monitoring units for historical biomonitoring studies.

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Keywords: Deer, Environmental fluoride, Fluoride in bone.

Source: Arch Environ Contam Toxicol 2000 Jan;38(1):121-7.

Personal fluoride and solvent exposures, and their determinants, in semiconductor manufacturing

Personal air sampling for fluorides and solvents was done at 35 semiconductor fabrication facilities in the United States. Fluoride compounds were used in etching and cleaning operations, and solvents were used in photoresist and developing operations. All personal solvent and fluoride levels were less than 2 percent of current Occupational Safety and Health Administration

(OSHA) standards. Statistical models of the exposure determinants for the target agents found production level, as indicated by number of semiconductor wafer cassettes loaded/unloaded from the target machines or baths, was predictive of fluoride, xylene and 1-methoxy-2-propyl acetate exposures. The percent of fresh air ventilation and the percent of xylene in the photoresist were also significant determinants in the statistical model predicting personal xylene exposure levels.

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 Keywords: Airborne fluoride, Environmental fluoride.
 Source: *Appl Occup Environ Hyg* 2000 Apr;15(4):354-61.

Structure and mineralisation density of antler and pedicle bone in red deer (*Cervus elaphus L.*) exposed to different levels of environmental fluoride: a quantitative backscattered electron imaging study

The structure and relative degree of mineralisation of antler and pedicle bone of yearling red deer stags exposed either to low or high levels of environmental fluoride were determined by digital quantitative backscattered electron (BSE) imaging. Bone fluoride content (BFC) in antlers (845 ± 86 mg F⁻/kg ash, arithmetic mean \pm S.E.M.) and pedicles (1448 ± 154 mg F⁻/kg ash) of deer from a highly fluoride polluted area in North Bohemia (Czech Republic) were significantly higher ($P < 0.001$) than those of controls from uncontaminated regions in West Germany (antlers: 206 ± 41 , pedicles: 322 ± 52 mg F⁻/kg ash). Mean ($56.5 \pm 4.5\%$) and maximum ($84.9 \pm 2.1\%$) mineralised bone area of the control antlers significantly ($P < 0.05$ and $P < 0.001$, respectively) exceeded the corresponding values for the N. Bohemian deer (43.3 ± 1.3 and $73.3 \pm 1.9\%$, respectively), while the pedicles from the 2 groups did not differ significantly. In the pooled antler samples ($n = 18$), negative correlations existed between BFC and mean ($r(s) = -0.62$, $P < 0.01$) as well as maximum ($r(s) = -0.69$, $P < 0.01$) mineralised bone area. Morphological imaging revealed a decreased width and an increased porosity of the antler cortex in the N. Bohemian specimens. Mean (148.5 ± 1.7) and maximum (154.2 ± 1.7) BSE-signal intensities (= grey levels; range between a monobrominated (grey level 0) and a monoiodinated (grey level 255) dimethacrylate resin standard) of the antlers from the controls were significantly higher than those of the N. Bohemian deer (140.7 ± 2.1 and 145.7 ± 2.2 , respectively; $P < 0.05$ for both comparisons). In the pooled antler samples, negative correlations between BFC and mean ($r(s) = -0.51$, $P < 0.05$) as well as maximum ($r(s) = -0.52$, $P < 0.05$) BSE-signal intensities were observed. No significant differences in mineralisation density parameters were found for the 2 pedicle samples, and BFC and mineralisation density of the pooled pedicles were uncorrelated. Morphological imaging revealed bone mottling (denoting increased remodeling activity) and frequent occurrence of ap-

parently increased osteocyte lacunae in some of the pedicles from the N. Bohemian deer. It is concluded that the reduced amount of mineralised bone in, and the lower mineralisation density of, the N. Bohemian antlers resulted from a fluoride induced disturbance of bone mineralisation. The rapid growth of antlers leads both to a high mineral demand and a high rate of fluoride uptake during antlerogenesis. This, and the limited lifespan of antlers, which does not allow for a compensation of a delay in the onset or progression of the mineralisation process, renders antler bone particularly susceptible to fluoride. Antlers are therefore considered a useful model for studying fluoride effects on bone formation. Furthermore, analysis of cast antlers enables a noninvasive monitoring of environmental pollution by fluorides.

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Keywords: Deer, Environmental fluoride, Fluoride in bone.

Source: *J Anat* 2000 Jan;196 (Pt 1):71-83.

Sulfur hexafluoride: global environmental effects and toxic byproduct formation

This work provides information concerning possible global environmental implications and personnel safety aspects that should be considered during the commercial uses of sulfur hexafluoride (SF₆). SF₆ is an anthropogenically produced compound, mainly used as a gaseous dielectric in gas insulated switchgear power installations. It is a potent greenhouse gas with a high global warming potential, and its concentration in the earth atmosphere is rapidly increasing. During its working cycle, SF₆ decomposes under electrical stress, forming toxic byproducts that are a health threat for working personnel in the event of exposure. Several precautions are recommended to avoid personnel exposure to toxic byproducts: oxyfluoride levels or other byproduct concentrations in the operating gas matrix should be traced to predetermine the overall gas toxicity; contaminants should be systematically considered during maintenance, chamber evacuation and system opening process; small SF₆ quantities leaking into air or stagnated pollutant concentrations in the operating field should be analyzed and compared to the threshold limit values and permissible exposure levels. New system design rules (i.e., hermetically sealed gas compartments, gas recycling or disposal in the field area) and different handling policies – both during maintenance and final disposal – now should be considered globally to provide for environmental and personnel safety.

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Keywords: Airborne fluoride, Environmental fluoride, Sulfur hexafluoride.

Source: *J Air Waste Manag Assoc* 2000 Jan;50(1):137-41.

Urinary fluoride as an exposure index in aluminum smelting

Urinary fluoride was evaluated as an exposure index for a prospective study of asthma in an aluminum smelter. Two studies were conducted to evaluate the relationship between airborne exposure and urinary excretion over a workweek, and to describe exposures among jobs and over time. Thirty-two subjects were evaluated on Days 1 and 3 of a 3-day workweek. On each day, spot urine samples were collected prior to the start of work and again at the end of the shift. Samples were analyzed for fluoride and expressed as milligrams fluoride per gram of creatinine. Airborne exposures to total particulate, fluoride particulate, and hydrogen fluoride (HF; using a 37-mm filter cassette containing a filter and treated back-up pad) were also evaluated on each subject. In the second study, postshift urine samples were collected from asthma study volunteers in three surveys extending over 1.5 years and analyzed for fluoride. Average airborne exposures were 15.7, 4.1, and 0.7 mg/m³ for particulates, particulate fluorides and HF, respectively, and were substantially higher among carbon setters than other workers. However, average urine fluorides among the same workers were reasonably low, 1.3 and 3.0 mg/g creatinine in pre- and postshift urine samples, respectively. Carbon setters, who routinely wore respiratory protection during high exposure periods, had urinary fluoride levels similar to those of other potroom personnel. A significant variation in dose, as expressed by postshift urinary fluoride levels, was observed between potroom and non-potroom jobs and over three survey periods. These results suggest that postshift urinary fluorides provide a reasonable exposure index for surveillance of exposure levels for an epidemiologic study, and that a substantial variation of exposure occurs between jobs and over time. Although urinary fluorides may be used for exposure surveillance, additional details on individual exposure agents and patterns of exposure over time are required for complete assessment.

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Keywords: Airborne fluoride, Aluminum, Environmental fluoride, Fluoride excretion in urine.

Source: AIHAJ 2000 Jan-Feb;61(1):89-94.

BIOCHEMICAL EFFECTS

Ontogeny of G-protein expression: control by beta-adrenoceptors

Cardiac cell homeostasis is maintained in the face of excessive beta-adrenoceptor stimulation through the process of desensitization. Desensitization is not an inherent property of these cells but rather is acquired during development; neonates given beta-agonists actually show heterologous sensitization, involving changes in the expression and catalytic activity of adenylyl cyclase (AC) as well as an increased receptor/G-protein coupling. The current study examines the role of specific G-protein components, G(salpa) and

G(α), in the ontogeny of beta-adrenoceptor responses and in the transition from agonist-induced sensitization to desensitization. Between postnatal days (PN) 6 and 15 there was a significant decrease in the 52 kDa isoform of G(α) with no accompanying change of the 45 kDa form; over the same period, G(α 3) also declined substantially. In contrast, the 45 kDa isoform of G(α) and G(α 1,2) remained fairly constant over the same period and fluoride-stimulated AC activity increased. Treatment with isoproterenol on PN2-5 did not result in any significant changes in G(α) expression but robustly decreased G(α 1,2). These changes were accompanied by heterologous sensitization of AC activity at the level of AC itself, evidenced by equivalent increases in the enzymatic response to fluoride and forskolin-Mn(2+). Isoproterenol given to older animals (PN11-14) also caused specific loss of G(i) protein, in this case targeting G(α 3), whereas G(α) again was unchanged; in contrast to the younger group, the older animals displayed heterologous desensitization of AC at the level of G-protein function (specific loss of the fluoride response). These results indicate that the normal ontogenetic increase of cardiac beta-adrenoceptor coupling to AC is not dependent on the absolute amount of G-proteins, nor on the relative balance of stimulatory (G(s)) and inhibitory (G(i)) subunits. However, the ability of receptor stimulation to downregulate G(α 1,2), an event which is specific to immature cardiac cells, is likely to be an important component of the resistance of the fetal/neonatal heart to agonist-induced desensitization and hypertrophy. The maintenance of cardiac beta-adrenoceptor signaling in the face of intense stimulation is likely to play an important role in the physiologic adaptations necessary to the perinatal transition.

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Keywords: G protein, Fluoride.

Source: Brain Res Dev Brain Res 2000 Apr 14;120(2):125-134.

Two different mechanisms for activation of cyclic PIP synthase: by a G protein or by protein tyrosine phosphorylation

The biosynthesis of the functional, endogenous cyclic AMP antagonist, prostaglandylinositol cyclic phosphate (cyclic PIP) is performed by the plasma membrane-bound enzyme cyclic PIP synthase, which combines prostaglandin E (PGE) and activated inositol phosphate (n-IP) to cyclic PIP. The K_m values of the enzyme for the substrates PGE and n-IP are in the micromolar range. The plasma membrane-bound synthase is activated by fluoride, by the stable GTP analog GMP-PNP, by protamine or biguanide, by noradrenaline, and by insulin. The activation by protamine or biguanide and fluoride (10 mM) is additive, which may indicate the presence of two different types of enzyme, comparable to phospholipase C β and phospholipase C γ .

Plasma membrane-bound cyclic PIP synthase is inhibited by the protein tyrosine kinase inhibitor tyrphostin B46 with an IC₅₀ of 1.7 µM. However, the solubilized and gel-filtrated enzyme is no longer inhibited by tyrphostin, indicating that the activity of cyclic PIP synthase is connected with the activity of a membrane-bound protein tyrosine kinase. Cyclic PIP synthase activity of freshly prepared plasma membranes is unstable. Upon freezing and thawing of liver plasma membranes, this instability is increased about 2-fold. Protein tyrosine phosphatase inhibitors [vanadate, fluoride (50-100 mM)] stabilize the enzyme activity, but protease inhibitors do not, indicating that inactivation of the enzyme is connected with protein tyrosine dephosphorylation. Cyclic PIP synthase is present in all tissues tested, like brain, heart, intestine, kidney, liver, lung, skeletal muscle, spleen, and testis. Apart from liver, cyclic PIP synthase activity in most tissues is rather low, but it can be increased up to 5-fold when protein tyrosine phosphatase inhibitors like vanadate are present in the homogenization buffer. Preincubation of cyclic PIP synthase of liver plasma membranes with the tyrosine kinase src kinase causes a 2-fold increase of cyclic PIP synthase activity, though this is certainly not the physiological role played by src kinase in intact cells. The data indicate that cyclic PIP synthase can be activated by two separate mechanisms: by a G protein or by protein tyrosine phosphorylation.

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Keywords: Cyclic PIP synthase, Fluoride, G protein.

Source: Biol Chem 2000 Feb;381(2):145-53

Predominant contribution of the G protein-mediated mechanism to NaF-induced vascular contractions in diabetic rats: association with an increased level of G(α) expression

The purpose of this study was to determine the mechanism responsible for alterations in NaF-induced contractions of blood vessels from streptozotocin-induced diabetic rats. In the presence of AlCl₃, NaF (≥7.5 mM) produced significantly greater contractions in diabetic aorta and mesenteric artery compared with age-matched controls. Pretreatment with 1 µM nifedipine eliminated the enhanced contractile responses of diabetic vessels to NaF, resulting in no difference in the magnitude of NaF-induced contractions between control and diabetic vessels. In the presence of 100 µM deferoxamine, an Al³⁺ chelator, NaF-induced contractions of diabetic vessels were markedly attenuated, whereas only the responses to lower concentrations of NaF were reduced in control vessels. No significant difference was found in the peak amplitude of transient contractions induced by 10 µM cyclopiazonic acid between control and diabetic vessels. The addition of 10 µM okadaic acid produced attenuated contractions in diabetic vessels. These findings indicate no involvement of the inhibitory effects of NaF on endoplasmic reticular Ca²⁺-pump

ATPase and protein phosphatases in the genesis of the enhanced responsiveness of diabetic vessels to NaF. Western blot analysis showed a 2.5-fold increase in the expression of G(α) in diabetic aortic membranes. In contrast, the G(β) level was modestly decreased and the G(γ) and G(δ) levels were unchanged in diabetes.

The present results suggest that enhanced vascular contractions to NaF in diabetes is attributed predominantly to a G protein-mediated Ca^{2+} channel activation that results from markedly increased G(α) expression in vascular tissues under this pathological state.

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Keywords: Aluminum, Blood vessels, Diabetes, G protein, Sodium fluoride.
Source: J Pharmacol Exp Ther 2000 Feb;292(2):761-8.

Fluoride effect on the activity of enamel matrix proteinases in vitro

Dental fluorosis is common in individuals exposed to different sources of fluoride during tooth development. The mechanism causing this enamel defect is still unknown. Enamel matrix proteinases play a central role in the maturation of dental enamel, and inhibition of these enzymes by fluoride has been one explanation for dental fluorosis. We have investigated the effect of fluoride on the activity of enamel matrix proteinases using a colorimetric assay, casein zymography, and an enamel protein degradation assay. Fluoride (625 μM to 10 mM) inhibited neither the enzymatic activity of the crude matrix extract nor the activity of individual enamel enzymes separated by SDS-PAGE. The proposition that fluoride could directly inhibit enzymes was not confirmed in this study.

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Keywords: Dental fluorosis, Enzyme disturbances, Proteinases.

Source: Eur J Oral Sci 2000 Feb;108(1):48-53.

CORRECTION

In the abstract of the report by JV Kumar and PA Swango (*Fluoride* 1999; 32:256-7) on fluoride exposure and dental fluorosis in Newburgh and Kingston, New York, the word "Town" should have appeared after "Newburgh" in the last line of the abstract. The "city" and "town" of Newburgh are separate municipal entities.