FLUORIDE AND INTELLIGENCE

When observational data can be replicated consistently, they become relatively secure and less likely to be in error. On the other hand, the hypotheses and interpretations placed on data may vary considerably until a well-established theory emerges. In this issue of *Fluoride* is a further study linking fluoride and diminished intelligence, thus establishing more firmly that such a relationship exists.[1] However, hypotheses about the nature of this relationship are still tentative.

This new study from Tianjin, China compared children living in villages with a high, 3.15±0.61 ppm (mean±S.D.), or low, 0.37±0.04 ppm, level of fluoride in the drinking water.[1] The children with the high-fluoride intake had a lower mean IQ, 92.27±20.45, compared with the other children, 103.05±13.86. This difference of 10 points in IQ was significant ($P<0.05$). More children (21.6%) in the high-fluoride village had a retardation or borderline category of IQ than the children (3.4%) in the low-fluoride area. No confounding factors such as differences in social, educational, or economic background were present to explain the differences. These results are consistent with earlier studies indicating an IQ lowering of 8 to10 points in children living in villages with a high-fluoride intake from food or drinking water.[2,3]

These findings are also consistent with animal studies in rats, even though the rat is less sensitive to fluoride than man.[4] Increased exposure of rats to fluoride has been shown to produce neurotoxicity with sex- and dose-specific behavioural deficits.[5] Distinct morphological alterations in the brain, including effects on neurones and the cerebrovasculature, have been found after the chronic administration of aluminium fluoride and sodium fluoride in the drinking water.[6,7] Changes have also been recorded in cerebral phospholipid and ubiquinone levels with chronic fluorosis.[8]

Biochemical studies have identified mechanisms whereby fluoride could affect cerebral function. Fluoride is able to form a strong hydrogen bond with the amide group.[9] Enzymes could thus be altered in shape with reduction in activity. Aluminofluoride complexes stimulate various guanine nucleotide binding proteins (G proteins).[10] These metallofluoride complexes may thus mimic or potentiate the action of numerous extracellular signals and significantly affect many cellular responses. Fluoride ions in the presence of trace amounts of aluminium are apparently able to act with powerful pharmacological effects.

G proteins couple membrane-bound heptahelical receptors to their cellular effector systems.[10] When an agonist binds to the cell-membrane receptor, the G protein α subunit facilitates the exchange of the GDP bound to it for GTP, and the activated α subunit is then able to interact with effector enzymes such as adenylate cyclase or phospholipase C. The aluminofluoride complex thus acts as an analogue of GTP because the Al-F bond length is close to the P-O phosphate bond length. Both structures are tetrahedral. Fluoride and oxygen have nearly the same size and the same valence orbitals. Although fluorine as such does not hydrogen bond, it does so strongly as the fluoride ion and in HF, but not in R-F compounds, where electrons in covalently-bound fluoride are held more tightly than in covalently-bound oxygen. The carbonyl oxygen in amides is strongly polarized by resonance to behave in the direction of $R\text{-}O^{-}$, like alkoxides and the hydroxide ion, both of which are very strong proton and hydrogen-bonding attractors. Aluminium is close to phosphorus in the periodic table, and their valence electrons are in the same third shell. A high concentration of fluoride ions in solution induces the formation of a soluble tetracoordinated state of aluminium, which has almost the same geometry, size, and coordination as phosphate. Fluoride activation is used in laboratory investigations as evidence for the involvement of a G protein in a system. Aluminofluoride complexes mimic the action of many neurotransmitters, hormones, and growth factors. They also affect the activity of a variety of phosphatases, phosphorylases, and kinases.

Studies on mice have shown that fluoride and aluminium, individually and in combination, produced changes in the brain involving reductions in the concentration of the free-radical scavengers glutathione as well as reduced ascorbic acid and impairments in the activities of the protective enzymes superoxide dismutase, catalase, and glutathione peroxidase.[11]

Consideration must also be given to whether fluoride toxicity is enhanced by iodine deficiency. Even more striking differences in IQ, in children aged 7-14 years, were found in the iodine-deficient area of Xinjiang.[12] Children in two areas had IQs 19 and 25 points lower than children in the control area. The children in the affected areas but not in the control area had subclinical cretinism. A relationship was present between the iodine and fluoride levels. In the control area the children used iodized salt or cooking oil and had a normal mean IQ of 96. In one study area (B) the mean IQ was 77 with the drinking water fluoride being 0.34 ppm and the drinking water iodine 0.96 μg/L. In the other study area (A) the mean IQ was 71 with 0.88 ppm fluoride in the drinking water and 5.21 μg iodine/L. Areas A and B were both iodine-deficient, but area A, with the higher level of both iodine and fluoride in the water, had a lower mean IQ than area B with a lower level of both fluoride and iodine. A high-fluoride intake therefore seems to exacerbate the central nervous system lesions of iodine deficiency.

The toxic effects of fluoride on the brain thus cannot be viewed in isolation. Iodine and fluoride have mutually interacting effects on both goiter and fluorosis in mice.[13] Changes occurred over time in the effects of fluoride on thyroid function in the mice. The initial stimulatory effect of fluoride on the mouse thyroid at 100 days was followed by an inhibitory effect at 150 days.[13] In children with iodine deficiency, 0.34 ppm of fluoride may be associated with a lowering of the mean IQ by 19 points and 0.88 ppm of fluoride with a lowering of the mean IQ by 25 points.[12] Maternal thyroid deficiency during pregnancy may adversely affect the subsequent neuropsychological development of the child with lowering of the IQ by 4 to 7 points.[14] In some other studies of fluoride and intelligence, the iodine status of the children was not stated.[1-3] No reports have been published of impairment of the IQ in children after exposure to high-fluoride levels where the iodine intake is documented as being adequate.

Dietary factors, such as an adequate iodine intake, may be protective against the cerebral and IQ effects associated with a high fluoride intake. Studies on the mouse have found that although withdrawal of sodium fluoride and aluminum chloride brought about a partial recovery of all the parameters studied, the administration of ascorbic acid, calcium, or vitamin E, alone or in combination, resulted in a more complete recovery from the toxic effects.[11] Recovery was more pronounced with the combination.

Thus a high-fluoride intake has been linked to a lowered IQ in children in China. Possible mechanisms underlying the association have been described, and the role of iodine deficiency should be clarified further. Until the factors involved are better understood, it is not possible to determine what the degree of risk is, for neurotoxicity, for children with adequate nutrition but with a high-fluoride intake.

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THIRD INTERNATIONAL WORKSHOP ON FLUOROSIS AND DEFLUORIDATION OF WATER

Chiangmai, Thailand, November 20-24, 2000

The Third International Workshop is being organized by the International Organizing Committee under the auspices of the ISFR, in collaboration with the Intercountry Centre for Oral Health (ICOH), and the Environmental Development Co-operation Group (EnDeCo). Further Information can be obtained from:

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FIRST ANNOUNCEMENT: XXIVth ISFR CONFERENCE

The XXIVth World Conference of the International Society for Fluoride Research will be held at Piazza Ohmi in Otsu, Shiga, Japan on September 4-7, 2001. The meeting will be hosted by Professor Kazusada Yoshitake and the Department of Oral and Maxillofacial Surgery of the Shiga University of Medical Science.

Otsu, the conference venue, is an attractive city situated alongside “Biwako”, Lake Biwa. Lake Biwa is Japan’s largest freshwater lake and was once called “Nio-no-Umi”, Sea of Grebes. It is located near the centre of Japan and from early times has been used for fishing and the transportation of goods.

Some 14 million people use its water every day and the people living around Lake Biwa and those in Kyoto and Osaka are dependent on it. Since ancient times, many writers were inspired by the city of Otsu because of its beautiful surrounding landscape.

Otsu has a rich historical heritage, and the traditions of a vibrant culture characterize the city. For a brief period thirteen hundred years ago, Otsu was the capital of Japan. Later when the capital was moved to Kyoto, Otsu developed into a gateway city to eastern Japan and as a centre for land and water transport. It also became a centre for Buddhism with many major temples such as the Enryakuji Temple located there. In the Warring States Period, about 500 years ago, Otsu was involved several times and many local Samurai had their names etched in history. During the Edo Period, from 1603 to 1868, Otsu was the largest gateway city between Tokyo and Kyoto. Since that time, Otsu has remained the capital city of Shiga Prefecture.

FURTHER INFORMATION

The second announcement will include the list of invited speakers, the overall conference program, directions for preparing abstracts, and information about accommodation. Requests for the Second Announcement and registration forms for the conference should be received by May 14, 2001. Please send requests for the second announcement and correspondence to:

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The Secretary General for the conference will be Associate Professor Gaku Yamamoto at the same address.