

Aluminium

Aluminium is truly ubiquitous, being the third most common element of the earth's crust and its most abundant metallic constituent. Although aluminium comprises approximately 7% of the earth's crust much of the aluminium-containing compounds in the environment exist in insoluble forms and are not readily available to biotic species. The solubility of the inorganic aluminium-containing salts varies considerably with pH, with solubility favouring highly acidic, and alkaline conditions. Indeed, at physiologic pH compounds such as AlCl_3 and AlOH_3 remain extremely insoluble and thus, for the most part, not bioavailable. Organic aluminium chelate compounds such as aluminium molybdate, however, possess significant solubility at physiologic pH and thus have much higher potential for toxicity.

Aluminium is widely used in many commercial products; for example, aluminium containing substances are added to many processed foods, aluminium salts are used as antacids and as coagulants in the purification of water supplies, and aluminium has been found to be an inexpensive and durable metal for use in food containers, wraps and cookware. The vast majority of ingested aluminium fails to be absorbed by the gastrointestinal tract. Aluminium, despite being ubiquitous, is not considered to be essential for life and the element is not known to be employed in any biologic process. Of ingested aluminium, only minute amounts are absorbed into the body through the gastrointestinal tract. Gastrointestinal uptake of aluminium is enhanced by parathormone, which also appears to enhance brain deposition. Most circulating aluminium is rapidly cleared by the kidneys with any residue being primarily deposited into bone tissues. Under normal conditions, extremely small amounts of aluminium are present within the nervous system tissues. The normal amount of aluminium present within human cerebral gray matter is less than $2\mu\text{g/g}$ dry weight of brain tissue.

Aluminium has long been known to be toxic to the nervous system when it was recognised that local application of aluminium containing compounds to the cerebral cortex of cats and rabbits could be used to induce seizures. Although there was difficulty standardising the model, seizures were generally initiated within 30-60 days. In 1965, Klotz and co-workers and Terry and Pefia reported simultaneously the induction of neurofibrillary degeneration in neurons underlying the area of direct exposure to the aluminium containing compound. The neurofibrillary changes induced by aluminium were initially considered by light microscopic criteria to be comparable to the human neurofibrillary tangles encountered in Alzheimer's disease and other disorders. Subsequent studies have shown that aluminium-induced tangles are primarily composed of hyperphosphorylated neurofilaments and to have a straight configuration rather than a paired-helical filament ultrastructural appearance of human neurofibrillary tangles.

Over the past 30 years, aluminium neurotoxicity has been extensively studied, primarily using rabbits. Prominent neurofibrillary degeneration develops within 1-2 days of injection into the cerebrospinal fluid (either intracisternal or intraventricular injection is most commonly used). Within 12-14 days, the neuronal changes are widespread, with prominent involvement of cerebral cortex, brain stem and spinal cord. The animals

show prominent hind limb weakness, muscular fasciculations and seizures, and generally die within 14 days. Acutely treated animals display loss of acquired conditioned avoidance, conditioned eye-blink responses, and other signs of short term memory loss. Through the use of metallic aluminium implanted into the subarachnoid space or repeated low doses, a more chronic model has been developed which generally shows more in the way of motor weakness.

Dialysis encephalopathy (also referred to as dialysis dementia) is a disorder associated with prominent aluminium accumulation in the central nervous system. This condition occurs in patients with renal failure who are undergoing chronic hemodialysis treatment and who are exposed to excess aluminium. The condition is characterised by the development of confusion, dyspraxia, myoclonus and grand mal seizures. Brain and bone tissues of affected patients show markedly elevated aluminium levels with aluminium content of cerebral gray matter frequently 10 times higher than normal. In affected patients, the aluminium accumulation in the brain has been linked to aluminium-containing, orally ingested, phosphate-binding gels or to aluminium contamination of the dialysate fluids. The disease is generally fatal within 6 months although patients with lesser degrees of aluminium intoxication may survive with less severe symptomatology for years and those treated with the chelating agent desferrioximine can show reversal of the condition.

In 1973, Crapper and co-workers reported the presence of elevated concentrations of aluminium in the brains of four individuals with Alzheimer's disease when compared to normal controls. Further studies determined the regional distribution of aluminium in additional brain specimens. They again showed an increased concentration of brain aluminium in cases of Alzheimer's disease with the highest concentrations originating from areas with the greatest numbers of neurofibrillary tangles. The various analytic approaches used to determine bulk brain aluminium concentrations are technically difficult and attempts at replication have yielded differing results. Using neutron activation analysis, a technique that provides very accurate assessment of trace element concentrations, Marksbery and co-workers reported no increase in aluminium content between brain samples obtained from Alzheimer's disease victims and controls.

Such bulk analytic studies were dealing with extremely small concentrations of aluminium and relatively small differences between affected tissues and controls. Furthermore, such approaches measure the aluminium content of the entire sample being analysed and cannot ask the question on the cellular or sub cellular level. In a situation where the accumulation of these elements were associated with focally distributed cellular lesions such bulk tissue analysis might fail to identify any significant differences. Recognizing this potential problem, Perl and Brody turned to a microscope analytic approach. Using the technique of scanning electron microscopy with x-ray spectrometry (SEM-XRS), they reported detecting aluminium accumulations within the neurofibrillary tangle bearing neurons in such cases and in controls did not show similar accumulations. More recently, Good and colleagues have used laser microprobe mass analyser or LAMMA to further define the subcellular localization of aluminium in Alzheimer's

disease tissues. The LAMMA provides extremely low detection limits for trace elemental analysis with very precise subcellular localisation. Using this technique they reported evidence of excess amounts of aluminium and iron in association with neurofibrillary tangles of Alzheimer's disease. Also employing the LAMMA method, Marksbery and co-workers failed to find similar evidence of aluminium excess in Alzheimer's disease neurofibrillary tangles; however, the two groups have used differing instrumental parameters and approaches to data collection and analysis.

Perl and colleagues have also used microprobe techniques to investigate the trace element content of tangle-bearing neurons identified from natives of the island Guam suffering from amyotrophic lateral sclerosis/parkinsonism-dementia complex. These studies initially identified similar aluminium accumulation in the tangle-bearing neurons using SEM-XRS. The presence of excess aluminium in these tangles of the Guam patients has now been confirmed using 5 different analytical methods.

LAMMA and SEM-XRS have also provided evidence of increased aluminium and iron content in the neuromelanin granules of substantia nigral neurons and Lewy body containing neurons of cases of Parkinson's disease. There is an extensive literature linking Parkinson's disease to excess iron and oxidative stress. Iron, through the action of the Fenton reaction, is capable of catalysing the production of highly reactive hydroxyl radicals from hydrogen peroxide, a by-product of dopamine metabolism. Aluminium, being a single valence (+3) does not itself promote oxidative reactions. However, it has been shown that aluminium, when present with iron, enhances the latter element's ability to induce lipid peroxidation through the Fenton reaction by almost ten fold. This suggests that in such neurodegenerative diseases, while aluminium may not directly be inducing a state of oxidant stress, its presence along with iron may further increase the tendency to produce oxidative damage.

An additional property of aluminium is its ability to complex with proteins. Aluminium has been shown to cause aggregation of the neurofilament proteins as well as the microtubule associate protein tau (the major constituent of the paired-helical filaments of man's neurofibrillary tangles). Such aggregation appears to impair proteolysis and in an in vitro system has been shown to induce β -pleated sheet formation. Despite all of the above, the precise role that aluminium might play in the pathogenesis of disease remains unclear. However, these findings would suggest that the element does play an active role in the process although its exact nature remains to be elucidated.

Further Reading

Clauberg M., Joshi J.G., (1993), Regulation of the protease activity by aluminium; implications for Alzheimer's disease. *Proc Natl Acad Sci USA* 9:1009-1012.
Good P.F., Perl D.P., Bierer L.M., Schmeidler J., (1992), Selective accumulation of aluminium and iron in the neurofibrillary tangles of Alzheimer's disease: a laser microprobe (LAMMA) study.