

ALUMINIUM, CHEMICAL PHYSIOLOGY, AND ALZHEIMER'S DISEASE

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ALUMINIUM is unquestionably neurotoxic: encephalopathy develops in some patients on long-term renal dialysis with aluminium-rich dialysate.¹⁻³ The aetiological role of aluminium in Alzheimer's disease is much more speculative; although the detailed pathological manifestations of the disease differ from those of dialysis encephalopathy, aluminium has been identified within diseased neurons and, co-localised with silicon as amorphous aluminosilicates, has been found as a "consistent feature" at the core of senile plaques.^{4,6} The presence of aluminium at these sites—whether as cause or consequence of disease—raises questions about the mode of its absorption and the mechanism by which it is transported within the physiological environment. The intake of aluminium is 20 mg/day (range 1–100) via the gastrointestinal tract and 3–15 µg/day (range 2–100) via inhalation, leading to a median plasma level of 7 µg/l (range 1.5–15).⁷ If aluminium is a causal agent in Alzheimer's disease it must be transported to and bound at a key site; another requirement is a process for amplification of biochemical damage so that profound changes are brought about by extremely small concentrations. We now draw attention to aspects of the chemistry of aluminium that may throw light on such issues.

CHEMISTRY OF ALUMINIUM

The ionic radius of Al^{3+} closely resembles that of Fe^{3+} and the hydrolysis behaviour of Al^{3+} and Fe^{3+} in aqueous solution are also very similar. The $[\text{Al}(\text{H}_2\text{O})_6]^{3+}$ ion, like $[\text{Fe}(\text{H}_2\text{O})_6]^{3+}$, exists only in very acidic solution ($\text{pH} < 3$); at more basic pH, $[\text{Al}(\text{H}_2\text{O})_5(\text{OH})]^{2+}$ and $[\text{Al}(\text{H}_2\text{O})_4(\text{OH})_2]^+$ are formed. Minimum solubility is determined by the formation of $\text{Al}(\text{OH})_3$ at pH 6.5. At more basic pH the aluminate ion, $\text{Al}(\text{OH})_4^-$, is formed and this is the predominant species at the physiological pH of 7.4. All these species interact with various physiological ligands, of which the most important are Fe^{3+} binding proteins, especially transferrin (2–3 g/l in plasma); citrate (0.1 mmol/l in plasma); phosphate (2 mmol/l in plasma and 10 mmol/l intracellularly); and silicic acid ($\text{Si}(\text{OH})_4$, 21 µmol/l in plasma as Si). Silicic acid is an important, although neglected, ligand since it is a normal component⁸ of plasma and tissue and amorphous aluminosilicates have been found at the core of senile plaques.

The relative binding strengths of the ligands will determine the pathway of aluminium in vivo and its competition with other metal ions such as Mg^{2+} . For example, the hexokinase reaction is the first step in the metabolism of glucose in which ATP-Mg is involved in the formation of glucose-6-phosphate. In vitro, aluminium inhibits this reaction by binding to ATP 10⁷ times more strongly than Mg^{2+} , forming inactive ATP-Al.⁹ However, activity is restored in the presence of citrate because citrate binds aluminium 20⁵ times more strongly than ATP. Citrate therefore prevents the formation of ATP-Al and allows the formation of the active ATP-Mg complex.¹⁰ This example

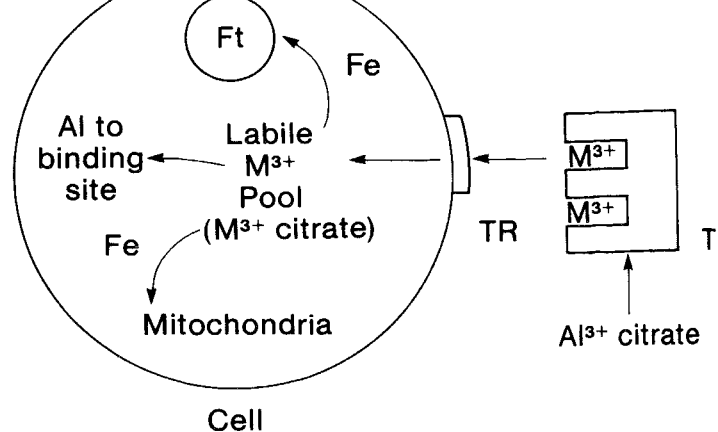


Fig 1—Aluminium and iron pathways.

Aluminium in plasma and extracellular fluid is ultimately bound in the iron transport protein transferrin (T). Iron and aluminium enter the cell via the transferrin receptor (TR) and both are held in the labile pool, probably by complexation with citrate. Iron is used in synthesis and excess is stored in ferritin (Ft), pathways not available to aluminium. Aluminium becomes bound to phosphate ligands such as vicinal phosphates on inositol.

illustrates the importance of relative binding strength in multicomponent systems.

Extracellular Metabolism

Aluminium follows the iron pathway in the extracellular environment in being bound to the iron transport protein transferrin and lactoferrin.¹¹ Stability of the aluminium complex with transferrin is believed to be less (approximately 10² times) than that of ferric iron ($\log K > 20$), but it is still high enough to suppress the interaction of aluminium with any other ligand in plasma (eg, OH^- , phosphate, silicic acid).¹⁰

Intracellular Metabolism

Once the metals are inside the cells, the difference between the two becomes apparent (fig 1). The chemistry of ferric iron and aluminium suggests that aluminium could coexist with iron in the cytosolic labile iron pool¹² (eg, with citrate as common chelator) but aluminium cannot be used, for example, by mitochondria, and ferritin will be unavailable as an efficient sink if the reduction of the metal ion (M^{3+}) to M^{2+} is necessary for entry into the apoferritin shell.¹³ The eventual fate of intracellular aluminium will therefore be to bind to sites that are stronger than cytosolic pool chelators such as citrate. At slightly acidic intracellular pH—at which cationic aluminium species are present—phosphate ligands are prime candidates and several types must be considered, including inorganic orthophosphate, ATP, and the phosphate groups of membrane lipophosphates and phosphorylated proteins. Cytosolic chelators such as citrate will dictate which of these ligands competes successfully for aluminium. When aluminium is present in equimolar solutions of orthophosphate and citrate at pH 6.6, over 97% of the metal is bound to citrate; when orthophosphate is replaced by ATP, 93% of the aluminium is bound to citrate; but when orthophosphate is replaced by inositol hexaphosphate, less than 10% of the aluminium is bound to citrate. A conclusion is that cytosolic aluminium