Aluminum Toxicity: Coordination and Interactions with Biomolecules

Alan Marumoto Literature Seminar April 5, 1988

Aluminum is the most prevalent metal in the earth's crust. Although much too reactive to be found abundantly free in nature, aluminum, chiefly in the forms of aluminosilicates and oxides, comprises 7.5% by weight of the earth's crust [1]. Nevertheless, aluminum appears to be non-essential to life; in spite of it's abundance, it is found only in extremely low tissue concentrations in healthy people [2].

However, when the tissue concentration of aluminum rises, aluminum toxicity may result. This toxicity is due to the effects of the octahedral hexahydrates species, $Al(H_2O)_6^{3+}$. Two important factors can affect the absorption of aluminum; the solubility of aluminum ions and the proportion of the toxic species. At low pH, both the total solubility and also the proportion of the toxic species are high. Refer to the diagrams below (Figures 1 and 2) [3]., I will refer to Al^{3+} as just aluminum from now on.

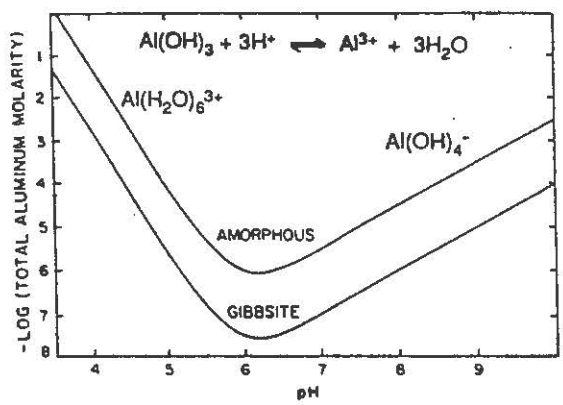

Figure 1

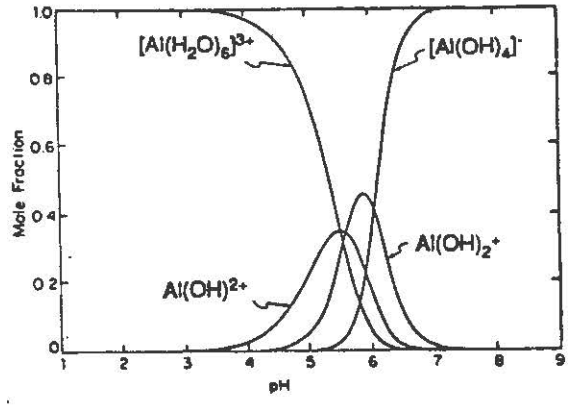

Figure 2

In some diseases, aluminum is significantly concentrated at very specific locations. In some cases, the disease and the symptoms directly result from the elevated aluminum concentrations. For example, the bone aluminum concentrations are significantly higher in patients with osteomalacia [4]. Similarly, in patients with dialysis dimentia, the brain levels of aluminum are significantly high [5]. In many other cases such as Altzheimers Disease (AD), Down's syndrome, and Amyotropic Lateral Sclerosis (ALS) there is also an increased level of aluminum in the brain. Unfortunately, it has not been demonstrated whether the aluminum accumulation causes the disease or whether the build up is just a secondary effect [6].

The bioavailability of aluminum is quite variable. Aluminum can be absorbed by lungs, through the gastrointestinal tract or directly into the blood [7]. The amounts absorbed by each of these processes depends upon various physiological and environmental factors [8].

The absorption of aluminum appears to occur via two mechanisms. One possible mechanism is the iron (III) absorption pathway because aluminum shows a high affinity for both ferritin (the iron storage protein) and transferrin (the iron

transport protein in the blood [9]. The second involves the formation of uncharged chelated aluminum species which can cross membranes. The chelator of aluminum appears to be citrate [10].

Citrate, a very common organic acid found in a variety of foods, forms primarily a 1:1 complex with aluminum at physiological concentrations. Complexation not only increases the total aluminum solubility, but at low pH (such as that in the stomach) the Al-citrate species is uncharged and thus has the can cross membranes [11] (Figure 3).

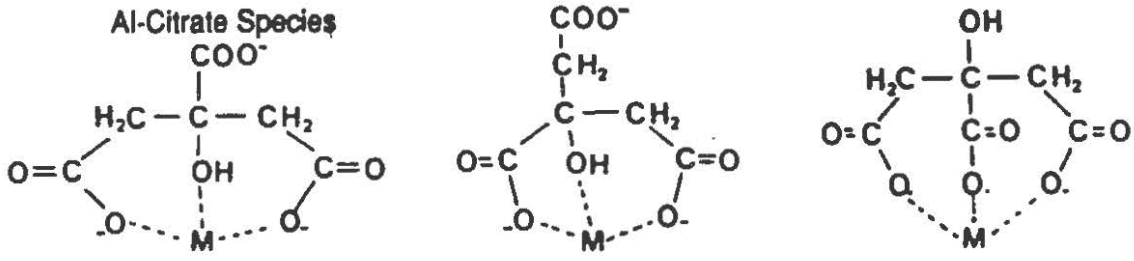

Figure 3

Once in the blood stream, citrate bound aluminum can get transferred to the unbound iron (III) binding sites in transferrin [12]. Since transferrin has a higher affinity for aluminum and is found in about the same concentration as citrate, transferrin proves to be the major aluminum carrier in the blood stream [13].

Aluminum can affect organisms in many ways. There are many non-specific effects such as the binding of aluminum to Deoxyribonuclic acids (DNA) [14], to membrane surfaces [15], to Adenosine Triphosphate (ATP) [16], and to proteins [17]. Since aluminum toxicity has been shown to have specific symptoms, more specific mechanisms are being investigated.

Since aluminum deposites are found in the brain, many mechanisms currently being investigated are related to neurology. A simplified view of chemical neurotransmission has a transmitting cell, a receiving cell and a gap between them called the synapse. The signal is transmitted by releasing the contents of a vesicle containing acetylcholine (ACh) from the pre-synaptic side into the synapse. The ACh diffuses across the synapse and binds to the acetylcholine receptor (ACh receptor) on the post-synaptic side. The excess ACh is hydrolyzed by the enzyme Acetylcholine Esterase (AChE) into acetic acid and choline. The hydrolyzed species can be reabsorbed and recycled by the transmitting cell (pre-synaptic) [18].

Neurotransmission can allegedly be stopped or inhibited at a variety of locations. The transmitting cell, for example, can be stimulated by such neurotransmitters as Dopamine (DA), Epinephrine (Epi), Norepinephrine (NE), γ-amino butyric acid (GABA), and enkephalins. Each of these chelates aluminum; thus transmission can be stopped before it starts [19].

Aluminum can also allegedly inhibit the transmission across the synapse. The first method is non-competitive binding and inhibition of the AChE [20]. The second method is the binding to the presynaptic membrane (making it more

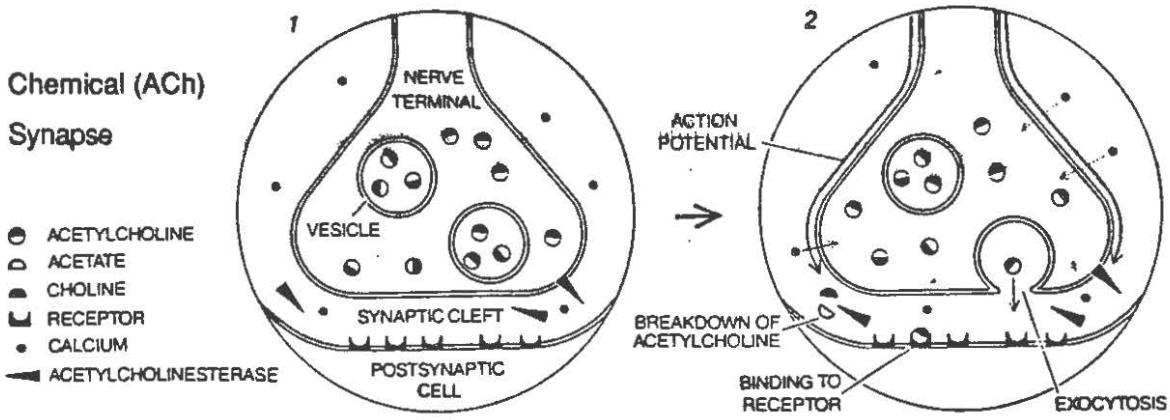

Figure 4

rigid) and thus inhibiting the release of ACh and the reuptake of the hydrolyzed components [21].

Should the signal be received by the post-synaptic cell, the chemical signal must still be translated into an electrical signal in order to be transmitted to the next synapse. Two important regulatory proteins of this process, calmodulin (CAM) and the G-protein, appear to be affected by aluminum.

Calmodulin's normal function is to be a intracellular messenger by turning on or off a variety of enzymes. When CAM binds 3 aluminum ions, its conformation is altered [22] and its ability to turn on cyclicAdenosine Monophosphate (cAMP)phosphodiesterase is inhibited [23].

The G-protein is activated by the binding of GTP, and is deactivated when the GTP is hydrolized to GDP and inorganic phosphate (P_i). Aluminum binds fluoride anion very tightly to form AlF_4^-. This anion binds well to the GDP-G protein complex (in vitro) tricking the G-protein into thinking it is being bound by a GTP instead of a GDP. Since the AlF_4^- cannot be hydrolyzed, the G-protein remains "ON" and continually produces cAMP [12].

The moleoular mechanisms of Altzheimers, Down's syndrome and ALS have not been proven. However, should the mechanism prove to be aluminum toxicity, then inorganic chemistry and medicine will once again overlap as in the case of Wilson's disease and the development of the copper chelator penicillamine [24].

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