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Aspects of the bioinorganic chemistry of aluminium(III) relevant to the metal toxicity

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CONTENTS

To what risks are we exposing ourselves especially in older age? What can the inorganic chemist say about the biochemistry of aluminium? [1]

A. INTRODUCTION

An extensive and articulated body of information demonstrates that Al(III) is a toxic metal centre. In fact, abnormal exposure to Al(III) is recognized as an etiological factor in aluminosis [2], dialysis, encephalopathy and osteodistrophy [2,3], and non-iron deficiency microcytic anaemia [4]. Moreover, analytical observations [5] and epidemiological data [6] point to an implication of abnormal accumulation (and uptake?) of Al(III) as a significant marker of Alzheimer's disease.

Convincing evidence for the international scientific awareness of the implication of Al(III) in biological systems is offered by the exponential growth of the number of papers appearing in the period 1970–1990 (Fig. 1) and quoted in Biological Abstracts.

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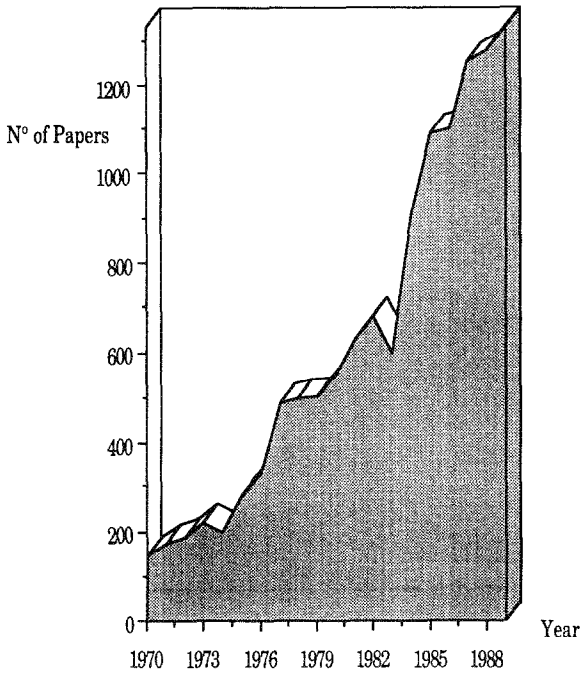


Fig. 1. Plot of the number of papers on various aspects of Al(III) biology vs. time in the last two decades. (data from Biosis).

Very extensive in vivo toxicological work has revealed that artificial exposure to Al(III) causes well-defined neurotoxic [7], cardiotoxic [8] and hepatotoxic [9] effects in rabbits. In vitro tests have recently provided evidence for both cytostatic-differentiating and cytotoxic effects of diverse chemical forms of Al(III) on murine neuroblastoma cells [10].

It must be emphasized that a conceptual basic drawback in the interpretation of the toxicological data, even at a phenomenological level, lies in the ill-defined character of the aluminium species administered at physiological pH values in the absence of strongly complexing agents [11]. Of course, the same problem affects interpretation of the rather extensive body of enzymological data available to date [11,12]. In this connection, biological and toxicological experimentation carried out in these laboratories [8,10,13] is providing evidence of dramatic speciation effects in the response of biological targets to aggression by Al(III). In fact, the nature of the coordination sphere of Al(III) (i.e. its speciation) is found to *direct* both the *type* of biological effect and, when these turn out to be speciation-independent, the *intensity* of a given biological response [10(b)].

Although extensive and sometimes contradictory [14] information on the bonding interaction of Al(III) with biologically relevant carboxylate and catecholamine ligands is available [11], all these data are generally thermodynamic in nature rather

than structural. Two noticeable exceptions are the X-ray single crystal molecular structures recently determined for $Al(lact)_3$ [15] and for $[NH_4]_5[Al_3(H_1\text{-}Cit)_3(OH)(H_2O)]NO_3]\cdot 6H_2O$ [16] (Cit = citrate). Moreover, the thermodynamic information mentioned above refers to acidic aqueous conditions which are required to ensure kinetic feasibility for the potentiometric methodology employed to obtain them.

On the other hand, information on the interaction of the metal centre with potentially ligating sites (vide infra) present in biologically relevant small molecules such as nucleobases, nucleotides, ATP, small peptides, amphiphilic molecules, relevant to (or model for) biological membranes is scanty from a structural point of view. These data, as well as data on the interaction of Al(III) with purified DNA, transferrin and calmodulin, will be reviewed in this paper, with particular attention to the molecular aspects of the metal–biomolecule interaction. The aim of this review is to select from a very extensive and entangled toxicological, biological and chemical literature, the papers which deal with structural observations relevant to the interaction of Al(III) with biomolecules.

For a better evaluation of the relevance of the individual following paragraphs to the general problem of Al(III) toxicity, a schematic representation of the metal metabolism in humans is given in Fig. 2. Aluminium(III) gains access to the human body via inhaled dust, food and beverages, water, drugs, cosmetics, etc. Most of the metal is excluded from the major organs by the intervention of the gastrointestinal

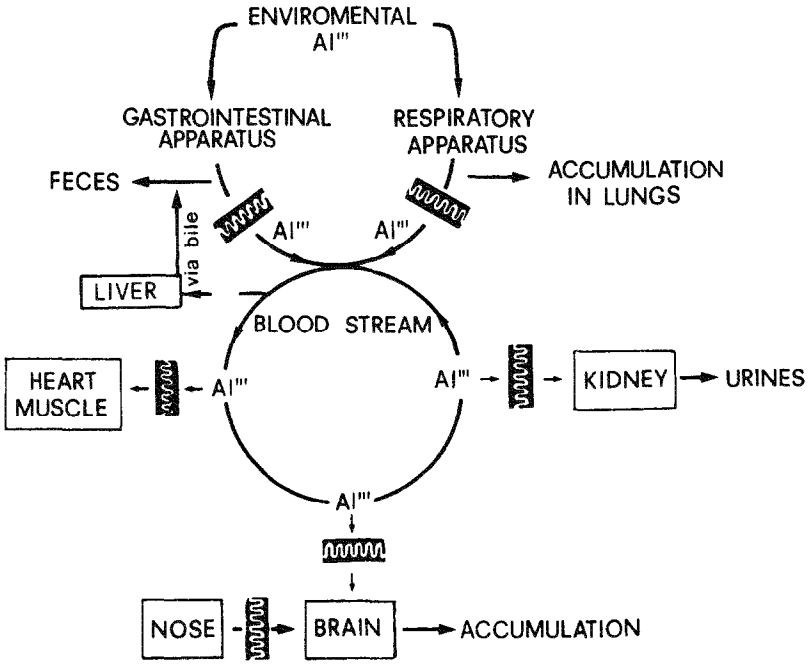


Fig. 2. Metabolism of aluminium in humans.

barrier and by correct renal function (see below). However, a little but significant accumulation occurs in the whole body, including the brain.

B. SPECIATION OF Al(III) IN WATER AND BIOLOGICAL FLUIDS

In the absence of complexing agents, the most reliable literature data [17] lead to the following prediction of aquo and hydroxo species of Al(III) at pH 7.4 (μ = 0.6 M) in equilibrium with amorphous solid $Al(OH)_3$:$Al(OH_2)_6^{3+}$ (10^{-13} M), $Al(OH_2)_5(OH)^{2+}$ ($10^{-11.12}$ M), $Al(OH_2)_4(OH)_2$ ($10^{-9.50}$ M), $Al(OH)_3$($10^{-8.10}$ M), $Al(OH)_4^-$ ($10^{-6.86}$ M) (the concentration of oligomeric species is less than 10^{-22} M).

It must be strongly emphasized that this prediction is based on the assumption of equilibrium conditions between solid $Al(OH)_3$ and all the species mentioned above. In fact, at pH values around neutrality, the kinetics involving any Al(III) species are generally slow and the attainment of equilibrium conditions is far from being a normal condition when solid $Al(OH)_3$ is suspended in water [18]. In conclusion, any real (i.e. experimental) solution in equilibrium with solid $Al(OH)_3$ is, in fact, an ill-defined system as far as the exact speciation of the metal centre is concerned.

In biological fluids, the speciation of Al(III) is further complicated by the expected distribution of the metal centre in some broad classes of compounds: (i) aquo, hydroxo or aquo-hydroxo species, (ii) complexes with carboxylates (mainly citrate), (iii) complexes with metallo-proteins (transferrin), (iv) complexes with plasma non-metallo-proteins, such as albumin, (v) adducts with nucleotides triphosphates, and (vi) complexes with catecholamines.

C. Al(III)/MODEL-MEMBRANE AND MEMBRANE MOLECULES

It is known that Al(III) is capable of inducing alterations in vivo in the function of the plasmatic membrane of the endothelial cell which define the brain capillary vessels (blood–brain barrier, (BBB)) [19]. It is also known that Al(III) at μM levels induces phase separation, aggregation, dye release and membrane rigidification in phosphatidylserine and phosphatidylethanolamine containing lipid vesicles [20]. Moreover, we have discovered in our laboratories [13(a)] that Al(III) at mM levels induces in vitro a dramatic morphological effect (echino-acanthocytosis) on suspended rabbit erythrocytes. This effect is accompanied by a considerable reduction of membrane fluidity, as shown by ESR measurements after spin labelling [21]. In connection with this evident tendency of Al(III), in certain chemical forms, to "attack" biological membranes, it is worth mentioning that the aggression by exogenous or endogenous toxins to neuronal plasmatic membranes with consequent changes in membrane structure might be relevant to the etiology of various diseases [22] and to the development of cellular aging [23].

^{27}Al NMR spectra of Al(III) solutions interacting with a potassium dodecanoate

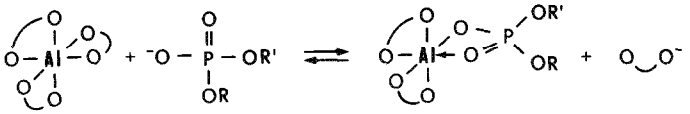
artificial membrane bilayer were interpreted [24] as being due to the reaction of $Al(OH_2)_6^{3+}$ with carboxylate head groups.

^{31}P NMR experiments are being carried out in our laboratories on a H_2O/triton/phosphatidylcholinedipalmitoyl/Al(III) system. The results collected so far reveal that $Al(acac)_3$ (acac = acetylacetonate) does react quantitatively (1 : 1) (Scheme 1) with the phospholipid molecules contained inside triton micelles at 40°C, this reaction being reversible with temperature in the 25–50°C range [25]. These data appear particularly interesting in that they could be relevant to the molecular bases of the biophysical effect caused by $Al(acac)_3$ on erythrocyte membranes described above.

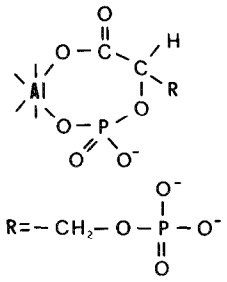
Aluminium(III) has been implicated as an etiological factor in non-iron deficiency microcytic anemia (microcytosis), which is a common syndrome among dialysis patients. The molecular bases of the Al(III)-induced disorder is unknown, but it may be related to the action of the metal centre with the cytoplasmatic site of the erythrocyte membrane. If this is the case, understanding the pathway for Al(III) transport from the plasma to inside the red cell wall will be a substantial piece of information for a possible therapeutic strategy. In this connection, 2,3-disphosphoglycerate has very recently been proposed as a potential carrier for trans-membrane Al(III) transport and is found to give a fairly stable 1 : 2(aluminium to ligand) complex, in which the carboxylate and one of the two phosphate groups are proposed to chelate the metal centre (Scheme 2).

D. Al(III)/NEUROLOGICALLY RELEVANT AMINES AND PEPTIDES

The elementary chemical aspects of the neurotoxicity of Al(III) to humans with impaired renal functions [2] and to experimental animals (mainly rabbits) [19] are terra incognita [7,19].



Scheme 1.



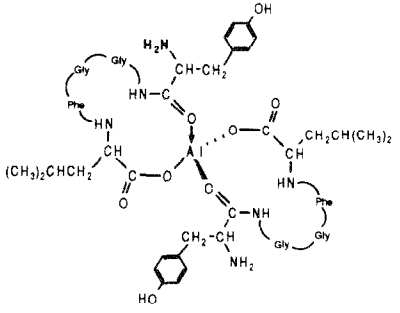
Scheme 2.

A reasonable chemical approach to a promising exploration appears to be, inter alia, the study of the coordination chemistry of neurologically relevant small molecules or peptides (i.e. potential cytosolic ligands) such as for example, those known or presumed neurotransmitters [27]. In this regard, the ligating potential of neurotransmitters such as dopamine, norepinephrine and epinephrine to $Al(OH_2)_6^{3+}$ was also evaluated [28] for AlL_3 species in terms of stability constants in water at 0.2 M ionic strength. The relevant conditional stability constants at pH 7.0 are fairly high and range from 10^{14} to 10^{16} and, on an indirect basis, metal coordination was considered to occur through the catecholate binding sites. However, no structural information on such Al(III) complexes appears to be available.

Spectroscopic work on this subject is also available [29], although it deals with DMSO solutions, which are questionable-models for aqueous systems. However, Al(III) (added as $Al(NO_3)_3 \cdot 9H_2O$) strongly binds to Leu^5-Enkefalin (Tyr–Gly–Gly–Phe–Leu), as shown by ^1H, ^{13}C and ^{27}Al NMR spectroscopy. The spectral data are interpreted on the basis of the formation of both 2:1 (**1**) and 2:2 (**2**) peptide–Al(III) complexes. Complex **1** has been proposed to be a tetrahedral species in which the Tyr^1 CO and Leu^5 COO^- groups are the Lewis basic sites. In complex **2**, one aluminium ion undergoes the same coordination mode as in **1** and a second one undergoes coordination via an NH_2 group belonging to a Tyr residue, thus giving rise to an interesting [30] aminosolvento and/or hydroxo octahedral complex (Scheme 3).

E. Al(III)/ATP

A possible molecular pathogenic event involving the coordination chemistry of Al(III) could be its undesired bonding interaction with ATP. ATP exists in the cell as a complex with Mg^{2+} and it is this form of the nucleotide which is the substrate for most ATP-utilizing enzymes. Aluminium(III) binds ca. 10^7 times more strongly to ATP than does Mg^{2+} [11] and the result of this competition (coupled with the



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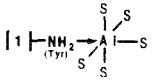

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Scheme 3.

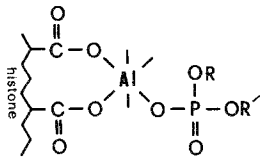
inertness of the ATP–Al(III) complexes at ca. pH 7.0) could well produce pathological conditions.

The reaction of Al(III) with ATP in water was investigated with multinuclear (^{1}H, ^{27}Al, and ^{31}P) NMR spectroscopy [31] in the pH range 1–12. The data at ca. pH 7 were interpreted as due to two stable complexes with 1 : 1 (**3**) and 2 : 1 (**4**) ATP/Al ratios. These two adducts appear to coexist in slow exchange rate with free ligand. Complex **3** should be, in fact, a dimeric 2 : 2 complex in which two aluminium ions are octahedrally surrounded by water or/and hydroxo ligands as well as by one phosphate ligand (at P_β and P_γ). Complex **4** was also proposed to be an octahedral species (^{27}Al NMR evidence) with two ATP molecules again coordinated via the P_β and P_γ oxygen atoms. A similar investigation is reported in ref. 32, confirming the observation described above. In neither ref. 31 nor ref. 32 was a detailed structural proposal for complexes **3** and **4** presented. Interestingly, no evidence of direct interaction of Al(III) with the adenine ring was obtained in the pH range 5–7.

F. Al(III)/CHROMATIN, PURIFIED DNA

Recent in vitro investigations on chromatin in rat cortical areas [33] came to the conclusion that Al(III) acts as a compacting agent at μM levels, thus causing chromatin precipitation and severe interference with the access of exogenous structural probes (e.g. nucleases) to chromatin itself. Moreover, experiments carried out on chromatin from intact nuclei of AD-affected brains offered evidence [34] that Al(III) markedly increases the affinity of histone H1° for DNA, thus suggesting its potential ability to inhibit the correct gene expression in vivo. This observation was interpreted as being due to the cross-linking action of Al(III) between histones, proteins, and DNA. The relevant bonds might involve two carboxylate ligands pending from a histone segment and a phosphate oxygen belonging to a DNA nucleotide (Scheme 4). This molecular hypothesis appears chemically rather reasonable in that it fits with very basic chemical events involving Al(III) and biomolecules presented so far.

The reactivity of Al(III) (1–10 μM) with calf-thymus purified DNA was also investigated by thermal denaturation, circular dichroism and fluorescent dye binding in the pH range between 5.0 and 7.5 [35]. Three distinguishable complexes are reported to predominate for Al:DNA ratios up to 0.7. The most biologically relevant one, i.e. that formed at neutral pH, was proposed to involve the bonding of



Scheme 4.

$Al(OH)(OH_2)_5^{2+}$ to DNA through the phosphate oxygen atoms. This complex can be dissociated with DNA regeneration upon treatment with EDTA. No detailed proposed structure was put forward in ref. 35 and further research work in this direction would be of great interest.

G. Al(III)/Mg(II)-DEPENDENT PROTEINS

In hexacoordinated complexes, Al(III) possesses an ionic radius which is not too different from those of Fe(III) and Mg(II), i.e. 0.54 vs. 0.65 and 0.72, respectively. Magnesium(II) is a co-factor of numerous enzymes, in particular those involving the phosphate transfer reaction. It is essential in maintaining the conformation of nucleic acids and it is considered important in regulating a variety of biochemical processes [36]. Thus, a possible Al(III)–Mg(II) competition for biological relevant ligating sites in biomolecules could be a fundamental source of pathological conditions [11(c)].

Aluminium(III) is also known to inhibit several Mg(II)-dependent enzymes [37] and the mechanism of this effect is not known, although in some cases Al(III) binding to allosteric and/or aspecific binding sites of some proteins has been invoked [11(c)].

H. Al(III)/IRON PROTEINS

According to various authors [37,38], most of the dietary and environmental uptake of Al(III) in healthy humans does not pass the normal gastrointestinal barriers. Indeed, about 1% of the metal reaches the blood stream and 90% of this amount is rapidly eliminated through the normal renal function. Aluminium in the blood (1.5–15 ppb) [39] is estimated to be complexed mostly by citrate and transferrin and the discovery of unknown carriers of the metal could be of great interest for the evaluation of possible risk factors for aluminium intoxication [40]. It is known [41] that transferrin binds only 30% of the total amount of Fe(III) which the protein could theoretically coordinate, so that it appears reasonable to hypothesize that ordinary transferrin (vide infra) could itself be a ligand [42] for Al(III) (Fe(III) and Al(III) possess a fairly close charge/radius ratio). This possibility appears particularly suggestive in the light of the circumstance that transferrin receptors are abundant at the blood–brain barrier level and they could be "innocent" mediators for the introduction of the toxin into the glial cells and eventually into the neurons. As a matter of fact, a specific affinity of Al(III) for transferrin has been clearly demonstrated by spectrophotometric titration [42] and by difference UV spectroscopy. In connection with this point, ^{67}Ga uptake experiments in the rabbit have demonstrated [45] that the major brain areas for the uptake of this tracer of Al(III) are the cerebral cortex and hippocampus, which contain the highest density of transferrin receptors and which are selectively vulnerable areas in Alzheimer's disease. The details of transferrin binding sites are not known with certainty, but they should be closely related to those of lactoferrin [46]. In this molecule, Fe(III) is bound to the protein through

the phenolate oxygen of two tyrosines, a carboxylate oxygen from aspartic acid and one neutral nitrogen atom from a histidine. It seems reasonable to admit that plasma biomolecules possessing a binding site electronically and sterically related to that of transferrin can be plausible candidates for an abnormal transport of Al(III) to the central nervous system. Of course, this possibility may become relevant to the pathogenesis of aluminopathies if these carriers would develop in concomitance with unhealthy conditions and/or human aging.

I. Al(III)/CALMODULIN

Calmodulin is an ubiquitous, evolutionary highly conserved, multifunctional, calcium-regulating protein build-up with 148 aminoacids, and is relatively abundant in the brain (about 10^{-5} M).

Bovine brain calmodulin was found [47] to bind three moles of Al(III) per mole of protein with a formation constant ranging from 10^6 to 10^7 M. EPR spectra of spin-labelled calmodulin gave indications that the action of Al(III) makes the protein more random and open. Moreover, calorimetric measurements suggested that the entrance of the first Al(III) is largely enthalpically driven. The same system was investigated [48] by fluorescence spectrophotometry and equilibrium dialysis. These experiments suggested that binding of Al(III) at a molar ratio of 2:1 produces major structural changes and that the Al(III) binding affinity to calmodulin is at least one order of magnitude stronger than that of calcium to its comparable site. Aluminium(III) coordination appears to induce a helix-coil transition with enhancement of the hydrophobic surface of the protein. At 4:1 molar ratio, the calcium-dependent phosphodiesterase is completely blocked.

Although this body of physico-chemical information indicates a clear interaction of Al(III) with calmodulin, a recent paper [49] presented results contradictory to some of the data reported in refs. 47 and 48. Remarkably, some of the experimental conditions of refs. 47 and 50 seem to be identical in terms of Al(III) speciation (i.e. pH and metal analytical concentration), but the protocols of the interaction of Al(III) with calmodulin appear rather different. In fact, the EPR effect described in ref. 47 refers to an Al(III)–calmodulin contact time equal to 24 h, whereas that depicted in ref. 50 seems to deal with much shorter contact times. In view of the circumstance that the solution state of Al(III) at pH 6.5 is, in principle, ill-defined [51], in the absence of strong coordination agents, the different effect of "total Al(III)" (vide infra) depicted in the two papers might stem from kinetic reasons [51].

The strong effects of Al(III) on such biologically important protein appears to be relevant in searching for chemical bases of aluminium toxicity. The structure of calmodulin [52] (Fig. 3) is safely established and the amino acid sequences involved in Ca(II) coordination have been synthesized and characterized properly [53]. It has also been hypothesized [54] that the effect of Al(III) on calmodulin could not be the consequence of Ca(II) displacement by Al(III) but rather of the formation of other

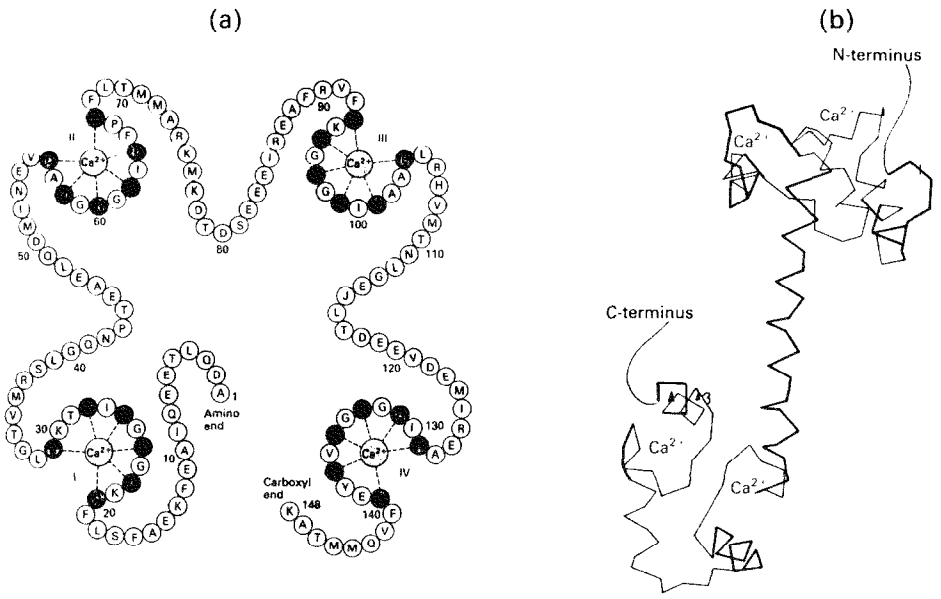


Fig. 3. (a) Schematic representation and (b) molecular structure of calmodulin. (Reprinted with permission from refs. 55 and 56, respectively.)
A, Alanine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; J, trimethyllysine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, theonine; V, valine; Y, tyrosine.

metallo-organic sites sufficiently stable to cause the effect described in refs. 47 and 48. An interesting evaluation of this possibility would stem from an investigation of the reactivity of the synthetic Ca(II) ligating sequences with Al(III). The inability of the metal centre to displace Ca(II) from this model complex would be strong bioinorganic evidence for the possibility outlined above and a way of access to an appropriate molecular hypothesis for interpreting the powerful "toxicity" of Al(III) to this fundamental Ca(II) regulatory protein.

J. CONCLUSIONS

Knowledge of the possible molecular bioinorganic basis of aluminium toxicity appears to be rather poor. Significant clues are available, but they are of rather limited scope. A great deal of bioinorganic work must be performed and targeted experiments devised in order to try to fill the gap between the knowledge of biological and biochemical phenomena and the molecular events from which they are generated. We envisage at least four main research lines to be pursued:

(a) reactivity of Al(III) with DNA-relevant small molecules (i.e. individual nucleosides and nucleotides);

(b) reactivity of Al(III) with simple molecules known to be related to the elementary

physiology of neurons and efforts aimed at elucidating the molecular structure of the relevant products;

(c) elucidation of the chemical basis of the biophysical effect of Al(III) on the integrity of the erythrocyte membrane, e.g. investigation on the reactivity of Al(III) with membrane-relevant phospholipids. In fact, this membrane could be an important model for throwing light onto more subtle and less easily detectable effects of Al(III) on the membranes of far more complex cells.

(d) investigation (and reinvestigation) on the effect of diverse Al(III) species on selected enzymes, especially those in which the structure and the function of the active site are properly elucidated and likely to display Lewis basic features suitable for Al(III) coordination (e.g. serine protease) [57].

A common feature of all this work must be the awareness [58] of the speciation of Al(III) under the neutral conditions typically utilised in biological and biochemical investigations.

ACKNOWLEDGEMENTS

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