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Recent aspects of aluminium chemistry and biology: a survey

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Contents

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1. Introduction

This paper is intended as an introduction to the following 19 papers on aluminium and its effects in biological systems. These papers are referred to by the first name author of each one and are readily found in the contents list.

Aluminium has been linked, somewhat tentatively only, to a number of diseases either as a direct causative effect or as an aggravating factor, yet it is, and has always been, as available as ferric Fe(III) is today in our present-day oxidative environment. Its availability increases rapidly with acidity and one of its well-known adverse effects is on plant life under acid rain conditions. If for no other certain reason this means that the continuous study of aluminium chemistry and the interaction of it with biological molecules in vitro and in vivo is a necessary precaution, and we are all grateful to Professor Zatta for organising this series of papers. The more we know the less we fear and the more we will be able to handle any problem with aluminium that is definitely diagnosed. I shall give here an overview of all articles so that an interested reader can readily find the matters that are of greatest concern for him/her. I treat articles according to their main common areas in the order, chemistry, in vitro biochemistry and in vivo biological studies, although many papers contain matter relating to all three sections.

2. New studies of aluminium chemistry

Essentially the chemistry of aluminium relevant to biological systems concerns the binding and its stability to organic molecules, their structures (since this affects uptake) and the ease of release of the metals ion from the complexes, as pointed out in the first paper by Yokel. While knowledge of chelation to molecules from organisms will be treated more generally in the next section, here we need to note our non-biochemical knowledge. Reading through this first paper and material in several other papers there appears to be little advance in principles from the treatments in the Ciba Foundation Symposium in 1992 [1]. However, there are many new stability constant data scattered in several papers. Of course, attention needs to be directed to the effective stability constants in biological circumstances, that is, outside the test tube. The major

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considerations apart from stability constants themselves are, therefore, competition from the proton at pH values from 7.3 down to quite acid conditions of animal digestive systems and of pH systems close to 5.0 in extracellular fluids of plants. When discussing the value of desferroxamine and hydroxypyridinones the pK_a values of the ligands and the known variation of stability with pH should be kept in mind as well as the binding constants and concentrations of other competing ions. It is reasonable to assume that aluminium (maybe at free ion concentrations of about 10^{-10} M at pH 7.3) will meet competition from Mg^{2+} and Ca^{2+} at $>10^{-3}$ M and for this reason binding to many carboxylate centres may be excluded from reach by Al^{3+}. Of course there is competition from the ubiquitous Fe^{3+} as well but here the relevant concentration of free iron is probably 10^7 times lower that that of free Al^{3+}.

The consideration of Al^{3+} complexes and of its precipitates has also to be taken in the context of multi-nuclear complexes of mixtures of ligands especially where one ligand is hydroxide. Here, very little is known about stability although many complexes are stable. The article of Schmidt et al. gives much structural knowledge about the complexes in comparison with similar Fe^{3+} compounds but while there is a strong suspicion that many such complexes of both iron and aluminium exist in soil and perhaps in organisms, there is no definite knowledge from model studies which is readily applicable to in vivo conditions.

3. The in vitro complexes of Al^{3+} with biologically produced ligands

Many of the ligands produced by organisms have also been studied in parallel with non-biological ligands and many of the same points can be made. There is not always sufficient data concerning effective constants under different conditions. Several articles in this collection address specific systems. A common problem is met in the description of citrate as a ligand of high pK_a and which may well form polynuclear complexes at particular pH values. In two papers Bodov et al., have used NMR to characterise Al^{3+}–citrate interactions. These papers relate nicely to that of Schmitt et al. in that they both analyse in great depth polynuclear Al complexes e.g. Al_3(citrate)$_3$(hydroxide). The first of the two papers by Bodov, Banyai, Zenkany and Troth, concerns a full description of the exchange kinetics of both metal ion and ligands and of functional features of different complexes determined using NMR. The second paper uses NMR parameters to characterise the structures. These in vitro studies are important since citrate is a major carrier of Al^{3+} in animal and plant circulating systems. The full value of the analysis needs of course a detailed examination of the effective stability constants in simulated biological conditions. We know that Al^{3+}/citrate/hydroxide reactions take days to come to completion so that there may well be many intermediate species which have critical properties but are not open to NMR or other structural studies.

The paper by Rubini et al. gives an over-view of many parallel binding and structural studies. In particular it stresses that effective binding constants are required over wide ranges of conditions. Not only multinuclear species complicate the picture but several ligands may be involved even when we examine small molecule association with aluminium. A telling description is given of the mononuclear complexes of Al with citrate, phosphate and hydroxide. However, many other potentially interesting situations are mentioned. We must remember that minority species may dominate when we turn to in vivo effects. A paper by Petrou while mentioning these problems draws attention to the ability of sugars, in particular D-ribose, to become associated with hydroxy-multinuclear complexes of Al. Here H-binding may be more important than direct complex formation, which is more dominant at very high pH.

4. Binding of Al^{3+} by larger molecules

The next series of papers I shall describe look at the interaction of Al^{3+} with larger chelating molecules from desferroxamine to proteins but including peptides, polysaccharides and polyphenolates. The smallest of these molecules is a peptide of seven amino acids with but two useful carboxylic acid centres, studied by Kiso et al. The data show that the peptide is as effective at binding as several smaller ligands even at pH 7.4. There are many peptides in cellular systems and I cannot help wondering how many are as effective as this one. Of course all such studies may be conceived as searches for therapeutic agents but then the problems of biological stability dominate—see the last section. The only protein studied and perhaps the one of dominant interest is transferrin. Harris and Messori determine both stability and kinetic data for binding of Al, Ga, In, Tl to this protein. All bind very strongly and undoubtedly this special Fe carrier is the most likely chelating agent for transport of Al^{3+} in animals. However, we must remember Al^{3+} retention (storage) by other high molecular weight materials such as phosphorylated proteins [3] bone and humic substances. The latter are described by Elkins and Nelson who use pH 4.0 in order to obtain comparable data of humic acid with many elements. The results are suggestive and it is undoubtedly true that these ill-characterised acids have an important role in the control of the availability of metal ions such as Al^{3+}. A notable feature of this paper is the wise use of ionic–covalent scales and not hard–soft characterisations of ionic properties in solution. Al^{3+} is not so selective due to its hardness but is so due to its small size [2].

5. Biological studies

Every paper in this series has some remarks relating to living cellular systems, yet much of the discussion leaves one with the impression that perhaps aluminium is of interest here and there but there is no clear-cut description of protection from excess of it. It is obvious that Al^{3+} has been available at around 10^{-10} M since the Earth cooled some 4.5×10^9 years ago. How has life failed to find a value for it? Was protection against it required and is it still required or can it be allowed to be a passive member of the environment? While in the articles there are considerations of simple model membrane systems, by Suwalsky et al. for example, an examination of the handling of Al^{3+} by simple cells, prokaryotes, is absent. Al^{3+} at pH 7.3 does not seem to affect either Mg^{2+} or Ca^{2+} in cellular reactions in any organisms. At high levels aluminium and its complexes do affect some transport systems so that exposure to these compounds should be avoided. It is considered by Suwalsky et al. that these effects are more likely due to interactions with membranes than with enzymes. On the other hand Lupidi et al., draw attention to the fact that Al^{3+} (in some form) does modulate proteolytic activities.

Moving to studies directly related to biological organisms the best place to start is with bioavailability. Here Berthon examines Al^{3+} intake into cells at various stages and also considers its excretion. A major part of the approach to this undertaking is to specify which complexes are most likely to be formed, and where, in a complicated multi-cellular organism. Naturally much of the data are complementary to that summarised in the first part of my article but Berthon makes the reader aware of the relevance of each complex to its likely environment. A detailed study of one particular biological fluid, human serum, is given by Sanz-Medel et al. They find that Al^{3+} transferrin is the major species present (80–90%) while low molecular weight citrate/phosphate complexes are likely to represent the remaining 15% of the Al^{3+}. These results confirm the impression given by the model studies described earlier. In passing it is worth noting that some plants appear to transport Al^{3+} as an oxalate (or citrate) complex in their more acidic circulating fluids. Oxalate is very useful as a low pH binding or precipitating agent since it has low pK_a values. The parallel biochemistry on Mn^{2+} and Ca^{2+} is intriguing and raises again the question of Al^{3+}/Ca^{2+} competition.

There are three papers on the vexed question of Al^{3+} and nerve toxicity, especially concerning brain diseases, but many other papers refer in passing to the problem which dominates all discussion of Al^{3+} in bio-systems—the relationship, if any, to Alzheimer's disease. Zatta et al., consider the question as to the likely influence of aluminium upon cell membranes which may well induce increase in oxidative damage hence they label Al^{3+} as a pro-oxidant in cells. If true then Al^{3+} is a direct toxic agent in neuron disease. This paper also relates to a study of model membranes by Di Noto et al., who discuss ligand–receptor interactions. By way of contrast Salifoglou discusses the possible role of carboxylate complexes in human diseases. This is largely a study of structures of potentially interesting model complexes but I include it here to show how very different is the thinking of different authors when they tackle Al^{3+} and disease. Zatta et al., see above, are mainly concerned with phosphated lipids. A particular worry I have is that there are also many phosphorylated proteins with high affinity for Al^{3+} and of course Al^{3+} is present in bone [3]. There is a lack of specificity of the Al^{3+} interaction with biomaterials once it has left the circulating fluids. Thus the problem of Al^{3+} toxicity could be referred to its more general effect on say iron homeostasis. This attitude is described by Crichton et al. with reference to brain diseases. In principle this is readily testable on cells in culture. A major problem is that homeostasis is based upon Fe^{2+} (and Al^{3+}).

In summary I have an uneasy feeling that the effects of Al^{3+}, often in doses exceeding those likely to reach the brain, are general and not specific. If true the interest in what Al^{3+} does, in a toxicity sense, may be impossible to tie down to particular metabolic activities. This may sound discouraging but it leads to greater pressure to find a suitable chelating agent to aid recovery by removal of Al^{3+} toxicity. Here recent efforts have been directed to the value of hydroxypyridinone complexes and it is a fitting closure to this section to refer to the paper of Santos on these chelates. They have the advantages of high binding constants and lipophilicity but of course such properties could aid distribution as well as simple excretion. As yet the value of these agents as drugs in combating a specific disease is not clear.

6. Aluminium in plants

Considering the known adverse effects of Al^{3+} on plant life, this group of papers should have included work of various groups on Al^{3+} mobilisation in soils, and uptake and circulation in plants, especially conifers. There is one paper by Flaten on the curiously high uptake of Al^{3+} into tea. Fortunately this paper is written in such a way as to illustrate the best ways of studying the effect of intake of aluminium in plant generally. The conclusion is that there is no known health risk, which again relates to the probably safe chelation of Al^{3+} in organisms.

7. Conclusion

From the time, more than 20 years ago, when Al^{3+} was considered to be toxic and affecting neurological functions—it is so when high doses reach the brain—to today, the advances in understanding the chemistry and in vitro biochemistry of Al^{3+} have been steady and this group of papers reports more gains in our knowledge. It is curious that studies in vivo have yielded very little gain. While one comes away with the general impression that cells have never allowed measurable concentrations of any free Me^{3+} ion to accumulate in them, not just Al^{3+} but Ga^{3+}, In^{3+}, Cr^{3+}, and even Fe^{3+}. As free ions—there are many potential binding sites should they gain access to organisms. If the toxicity is fairly general to lipids and proteins then describing it becomes exceedingly difficult. For this reason I missed an account of studies of effects of Al^{3+} on simple cells which can be manipulated in many different ways e.g. using genetics. Turning to therapy, the horny problems of the effects of silicate as a protective agent do not appear to have gained favour. It does seem to be that in most situations, combinations of proteins, especially transferrin, and phosphate and citrate are preferential. Of course silicate may be useful outside organisms to take up Al^{3+} as it does in many minerals. The source of highest organic ligand binding would appear to be phenols as in transferrin, hydroxypyridinone, some ferroxamins and humic acids (note this selectivity is not a choice of ‘hard’ Al^{3+} interacting with ‘hard’ acid but is overwhelming due to size selectivity. Al^{3+} is a very small ion and binds best to very small donors e.g. F^- and RO^- (phenolate) rather than $-CO_2^-$). Clearly, as is true of the study of other metal ions in organisms, much remains to be done to fully appreciate the way Al^{3+} affects living cells and the way in which it can be safely sequestered in higher organisms.

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