Morphologie (2016) xxx, xxx—xxx

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

ORIGINAL ARTICLE

The toxicity of aluminium in humans

La toxicité de l'aluminium chez l'homme

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KEYWORDS
Chronic aluminium intoxication;
Human exposure to aluminium;
Alzheimer's disease;
Breast cancer;
Autism spectrum disorders

Summary We are living in the 'aluminium age'. Human exposure to aluminium is inevitable and, perhaps, inestimable. Aluminium's free metal cation, $Al^{3+}_{(aq)}$, is highly biologically reactive and biologically available aluminium is non-essential and essentially toxic. Biologically reactive aluminium is present throughout the human body and while, rarely, it can be acutely toxic, much less is understood about chronic aluminium intoxication. Herein the question is asked as to how to diagnose aluminium toxicity in an individual. While there are as yet, no unequivocal answers to this problem, there are procedures to follow to ascertain the nature of human exposure to aluminium. It is also important to recognise critical factors in exposure regimes and specifically that not all forms of aluminium are toxicologically equivalent and not all routes of exposure are equivalent in their delivery of aluminium to target sites. To ascertain if Alzheimer's disease is a symptom of chronic aluminium intoxication over decades or breast cancer is aggravated by the topical application of an aluminium salt or if autism could result from an immune cascade initiated by an aluminium adjuvant requires that each of these is considered independently and in the light of the most up to date scientific evidence. The aluminium age has taught us that there are no inevitabilities where chronic aluminium toxicity is concerned though there are clear possibilities and these require proving or discounting but not simply ignored.

MOTS CLÉS
Intoxication aluminique chronique ;
Exposition humaine à l'aluminium ;
Maladie d'Alzheimer ;
Cancer du sein ;
Autisme et apparenté

Résumé Nous vivons actuellement à « l'âge de l'aluminium ». L'exposition humaine à l'aluminium est inévitable et, peut-être, inestimable. Le cation métallique libre de l'aluminium, $Al^{3+}_{(aq)}$, est hautement réactif biologiquement ; cet aluminium biologiquement disponible est un élément non essentiel mais il est essentiellement toxique. L'aluminium biologiquement réactif est présent dans le corps humain et cependant, mais rarement, il peut être extrêmement toxique ; on connaît moins de chose à propos d'intoxication chronique à l'aluminium. La question est posée ici de savoir comment diagnostiquer la toxicité de l'aluminium chez un individu. Bien que l'on ne puisse pas encore apporter de réponse sans équivoque à ce problème, il existe des procédures à suivre pour déterminer la nature de l'exposition humaine à l'aluminium. Il est également important de reconnaître des facteurs critiques dans les modes d'exposition et en

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http://dx.doi.org/10.1016/j.morpho.2015.12.003
1286-0115/

Please cite this article in press as: Exley C. The toxicity of aluminium in humans. Morphologie (2016), http://dx.doi.org/10.1016/j.morpho.2015.12.003

particulier que toutes les formes d'aluminium ne sont pas équivalentes sur le plan toxicologique et que toutes les voies d'exposition ne sont pas équivalentes dans l'apport d'aluminium aux organes cibles. Afin de déterminer si la maladie d'Alzheimer est le symptôme d'une intoxication chronique à l'aluminium pendant des décennies ou si le cancer du sein est aggravé par l'application topique d'un sel d'aluminium ou si l'autisme pourrait résulter d'une cascade immunitaire initiée par un adjuvant contenant de l'aluminium, il faut exiger que chacun de ces cas soit considéré comme indépendant à la lumière des plus récentes preuves scientifiques. L'âge de l'aluminium nous a appris qu'il n'y a pas de fatalité où la toxicité chronique de l'aluminium soit concernée bien qu'il y ait des possibilités certaines et qu'elles exigent la preuve ou l'actualisation des connaissances, mais non pas une ignorance des problèmes.

Introduction

What is it (which are the criteria) that we need to understand before we are able to appreciate fully the biological availability and hence possible toxicity of aluminium in humans? When, how and why is aluminium toxic in humans? We know that all interactions in vivo between biomolecules and aluminium are potentially toxic since we have no evidence of any benefit accruing from the body burden of aluminium [1]. However, our understanding to-date of the non-essentiality of aluminium does not preclude the possibility that novel aluminium biomolecule interactions do initiate or catalyse reactions as well as also preventing or slowing biochemical processes. Aluminium may have inadvertent benefits without commensurate essentiality. In elucidating roles for aluminium in human disease we have to unravel complex biochemical equilibria as part of a process of identifying specific and predominant biological effects caused, directly or indirectly, by aluminium.

A difficulty presented by aluminium is its high propensity to participate in biochemical processes and particularly through strong binding by oxygen-based functional groups [2]. This is a difficulty because it means quite simply that there are always myriad binding opportunities for aluminium in any one biological environment. These biomolecular interactions will involve binding of the free metal cation, $Al^{3+}_{(aq)}$, and an argument can be made that this is the predominant and perhaps only biologically available form of aluminium [3]. The argument then follows that all other forms or complexes of aluminium are quite simply vehicles for the delivery of $Al^{3+}_{(aq)}$ to target sites. The question might then arise as to what will be the expected phenotype or recognisable outcome of any such interactions with aluminium in a particular biological/physiological environment. Which of the many possible interactions with biomolecules will bring about the most significant or possibly most noticeable biological response? The predominant interaction, where most of a local burden of aluminium is occupied, might not be responsible for the pre-eminent effect of the total aluminium burden. What are the expected biological effects due to human exposure to aluminium? In answering this question for aluminium we need to take into consideration that when homeostasis of a specific biologically essential metal is disrupted there is often an expected phenotype in the affected environment. This might be manifested as symptoms of a deficiency or a sufficiency of the metal at local or global levels. We have extensive understanding of the biochemistry and physiology of essential metals and with this experience have emerged plenty of clues as to what to expect if such systems are not working as normal. In essence we can recognise relatively quickly and easily when human physiology is influenced by the unusual activity of an essential metal. Indeed the effects of many non-essential metals are also now more widely understood and are symptom specific, which means that attempts can be made to address their effects.

There is no true homeostasis where aluminium is concerned as there are no element-specific biological responses to its presence and its availability as $Al^{3+}_{(aq)}$ [4]. Aluminium is a silent, if not potentially highly disruptive, visitor to biological milieus, which means that it piggy-backs upon essential biomolecules hijacking both their form and function. The lack of any element-specific recognition leaves an open question as to what might be the tell-tale symptoms of chronic aluminium intoxication in humans. Emphasis is purposely placed on the term chronic, as acute toxicity of aluminium in humans is extremely rare and by definition generally non-specific in bringing about global cell, tissue and organ failure, dialysis encephalopathy [5] being the very best example of acute aluminium toxicity in humans.

Burgeoning human exposure to aluminium must now mean that most humans and certainly those living in the developed world, the aluminium age being a product of the developed world, are experiencing chronic intoxication by aluminium. Every cell or compartment in the body will, at any one time, be experiencing exposure to at least one atom of biologically reactive aluminium. The term intoxication implies actual toxicity but it is a point of definition as to when intoxication is actually manifested as toxicity. When and how is some element of human suffering recognised or acknowledged as a response to intoxication by aluminium? The robust nature of most biological processes means that coping mechanisms ensure their continuity even when under 'attack' by foreign invaders such as aluminium. However, even coping with the presence of aluminium will incur an energy deficit. Either energy will be expended in replacing something, which is directly affected by aluminium, for example the inhibition of an enzyme, or energy will be needed to cope with the physiological response to the presence of aluminium, for example, the expression of additional calcium-binding proteins in response to cellular excitotoxicity. Since energy is a finite resource in the body and energy currencies are also critical signalling systems then indirect effects of aluminium on these systems

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