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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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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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could produce unwanted and degenerative cascades elsewhere and throughout the body. Chronic tiredness could conceivably be a physiological response to the body burden of aluminium but which physician is going to attribute a state of lethargy in an individual with aluminium intoxication? By way of an example of the problem faced by physicians in diagnosing aluminium toxicity the question was recently asked as to how do we know that Alzheimer's disease is not the clinical manifestation of chronic aluminium intoxication [6]? While the question may perhaps be a little tongue in cheek there has not been any serious attempt to either answer it or indeed dismiss this as a possibility. The knee-jerk response to any question concerning aluminium and human health seems to be to dismiss the possibility rather than examining it systematically. What should be the approach when human exposure to aluminium is linked in some way to human disease?

Case studies: aluminium and Alzheimer's disease

The known facts about Alzheimer's disease are alarmingly stark. We do not know the cause of Alzheimer's disease and this deficit in knowledge has rendered its treatment, never mind its prevention completely ineffective. The little that is known about the disease points very strongly towards the environment as a major aetiological factor not only in purely sporadic forms of the disease but also where genetic predispositions are known to contribute to disease onset, progression and outcome. The major risk factor in Alzheimer's disease is ageing though such does not prevent many individuals living well into their ninth and tenth decades without displaying the Alzheimer's phenotype. Alzheimer's disease is a progressive neurodegenerative disease and includes accelerated neuronal losses, probably involving cell death via apoptosis, in initially specific regions of the brain before being manifested more globally in the latter and fatal stages [7].

The major risk factor for the body burden of aluminium is also ageing. The risk/ageing relationship is not linear in that there are periods before and immediately after birth and after entering the sixth decade when the propensity to retain aluminium in the body in general is greatly exaggerated. In both of these periods absorption of aluminium into the body is increased and elimination of aluminium from the body is decreased. Additionally there is evidence of genetic predisposition towards absorption, excretion and retention of aluminium, which combined with ageing, could identify a particular group with heightened sensitivity towards the body burden of aluminium [1]. Where the retention of systemic aluminium involves long-lived compartments such as bone in the periphery and neurones in the central nervous system the probability that aluminium might accumulate towards potential toxicity thresholds must become a reality. But what actually is a 'toxicity threshold' and what does it mean in respect of the human body burden of aluminium. Are toxicity thresholds quantifiable entities in that a critical concentration of aluminium and toxicity are reached simultaneously? We are in the habit of measuring the concentration of something in a tissue and then making a suggestion as to whether the concentration is significant from a toxicological perspective or not. Is this a valid approach to understand the possible toxicity of aluminium, for example in brain tissue?

To understand how aluminium might exert toxicity in a particular environment it is important to appreciate that the significant biological reactivity of $Al^{3+}_{(aq)}$ renders it a cation of choice for myriad potential ligands in that environment. If the majority of these interactions are with relatively benign ligands, for example, interactions with the cytosolic pool of citrate, then the sum of competitive equilibria for binding $Al^{3+}_{(aq)}$ may be insufficient to bring about any immediate biological response to the presence of aluminium, no toxicity phenotype. The sum of these competitive equilibria will determine the biological availability of aluminium and hence its toxicity in any particular environment. This is informative because it explains why there is not a threshold concentration of aluminium above which it is toxic but that such thresholds will vary considerably between different biological compartments each with their signature ligands for binding $Al^{3+}_{(aq)}$. While experimental evidence suggests that the aluminium content of brain tissue increases with age [8] this evidence must also point towards neurones as being the longer term repositories for aluminium and, significantly, that they can accommodate a burden of aluminium because neurones are home to many potentially benign (not overtly toxic) ligands for $Al^{3+}_{(aq)}$. This suggests that the brain burden of aluminium will not be manifested as toxicity until a critical and relatively high threshold is achieved, something, which for every day exposure to aluminium, would be expected to be reached over extended time periods, probably decades as opposed to years or shorter [9].

Case studies: aluminium and vaccines

So how can this understanding of possible aluminium toxicity in the brain explain the putative toxicity of aluminium adjuvants in vaccines? There is burgeoning evidence of autoimmune (for example, multiple sclerosis [10]), neuromuscular (for example, macrophagic myofasciitis [11]) and behavioural (for example autism spectrum disorders [12]) conditions being linked to exposure to aluminium adjuvants in vaccinations [13], including immunotherapy [14]. Immediately it should be clear that the form and mechanisms of exposure through vaccinations are unique in that the environment at injection sites [15] will be far removed from the slow build-up of aluminium, which is occurring over decades in neurones. The total aluminium arriving sub-cutaneously or intramuscularly in vaccines is high and its immediate interactions within the environment at the injection site are significant enough to deliver sufficient biologically reactive $Al^{3+}_{(aq)}$ to instigate the inflammatory reaction commonly seen as a reddening and swelling of the skin around the point of injection. This is aluminium toxicity! We still do not understand the acute toxicity of aluminium at injection sites but it is likely that the delivery of $Al^{3+}_{(aq)}$ by the adjuvant salt is sufficiently rapid to result in significant cytotoxicity with necrotic, hence the inflammation, cell death. How much of this cell death at the injection site is responsible for the adjuvant effect is also largely unknown but its efficacy in attracting infiltrating immunocompetent cells to the injection site adds an additional dimension to the

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response to aluminium. We now know that these infiltrating cells bite-off aggregates of aluminium adjuvant by phagocytosis and that the adjuvant is loaded into the cell cytosol in membrane bound endosome-like structures [16]. This process does not appear to be acutely cytotoxic, at least for the most commonly used aluminium adjuvant, AlHydrogel, which must also mean that these aggregates of adjuvant can now be carried away from the injection site towards lymph nodes and quite possibly to other sites in the body. So the observation that monocytic cell lines are able to load up their cytoplasm with 'aggresomes' of adjuvant without, it would seem suffering any immediate toxicity means that these same cells are capable of delivering a substantial 'load' of aluminium elsewhere in the body. This is a critical observation in our understanding of how aluminium might be transported throughout the body as it presents a potential mechanism for the delivery of a significant load of aluminium to a target site, such as the brain. An argument, which is often brought out with respect to the putative toxicity of aluminium in vaccines, is that the amount of aluminium injected is insignificant with respect to human exposure by other routes. However, this thinking does not account for what we now know unequivocally which is that significant amounts of aluminium adjuvant can be collected from injection sites and transported throughout the body and delivered in potentially acute amounts to target sites which would normally only receive or be subjected to very low but persistent exposure to aluminium. Recent evidence not only points towards the cellular trafficking of aluminium away from the injection site but also its potential delivery to the brain [11,17]. Imagine the potential catastrophic consequences of such for an infant receiving multiple vaccinations containing aluminium adjuvants during their first few months of life.

Case studies: aluminium and breast cancer

It should not now be difficult to appreciate that the route of exposure to aluminium can have critical implications for its putative toxicity [1]. The exposure regime is critical in our understanding of the possible role of aluminium in breast cancer. The environment is widely acknowledged as playing some role in the incidence and malignancy of breast cancer and while there is a link between the use of aluminium-based antiperspirants and the incidence of breast cancer it is not always easy to put a mechanism to this link [18,19]. The topical application of an aluminium-based antiperspirant to the underarm does result in an immediate and high reservoir of aluminium at the skin surface. This aluminium is an extremely effective antiperspirant and such efficacy can only be indicative of a direct inhibitory role of $Al^{3+}_{(aq)}$ on the activity of sweat glands [1,20]. While there is evidence that aluminium applied topically as an antiperspirant will permeate the skin and enter the blood [21] such transport of aluminium from the skin surface is not necessarily required either for its function as an antiperspirant or for any putative role in breast cancer. There is evidence that the aluminium content of breast tissue taken from individuals with breast cancer is higher towards the underarm region [22]. One explanation for this is that this region of the breast receives higher doses of aluminium as an antiperspirant and as such more aluminium accumulates in the breast tissue in this region. However, a complementary explanation is related to the fact that aluminium is an effective antiperspirant in or close to this region and that perspiration is an important, if not the most significant, route by which tissue/systemic aluminium is excreted from the body [23]. The implication is that the action of aluminium as an extremely effective antiperspirant could easily result in the build-up of aluminium within a tissue both because of its presence at very high concentrations at the skin surface and, specifically, an inability of that area of tissue to excrete aluminium through perspiration. It should be investigated if the local build-up of biologically available aluminium in the upper outer quadrant of the breast is a contributory factor in the higher incidence of metastases in this region. There are a number of potential ways that aluminium can be mutagenic including direct actions through its activity as a pro-oxidant [24] and indirectly as a genotoxin, something capable of altering gene expression at a local level [25].

So which criteria need to be considered if not fully understood before aluminium toxicity in humans can be diagnosed?

Examine the nature of an individual's every day exposure to aluminium considering both prominent and less obvious exposure regimes [1].

Identify activities, which are known to facilitate the excretion of aluminium from the body including exercise [23] and drinking silicon-rich mineral waters [26].

Estimate the body burden of aluminium in the individual through the measurement of urinary aluminium excretion and preferably over 24 h with and without imbibition of a silicon-rich mineral water [27].

Consider which further evidence might be helpful in supporting any diagnosis, for example, when possible, a tissue biopsy and a measurement of aluminium in the tissue [28].

Accept that biologically available aluminium is toxic wherever it is found in the body and that there are many ways that aluminium can be delivered to a target site where it can cause toxicity [29].

Remember that the nature of any exposure can be just as critical as the degree or amount of exposure. All routes of exposure are not equivalent and all forms of aluminium are not equivalent in the terms of their delivery of biologically available, $Al^{3+}_{(aq)}$, to target sites [3].

Disclosure of interest

The author declares that he has no competing interest.

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