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The Influence of the Environmental Metallotoxin Al(III) on Neuronal Cell Structures Linked to Neurodegeneration

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Abstract

Metalloneurotoxins are among numerous environmental factors strongly affecting cellular toxicity and endangering human health. Habitual and often-involuntary exposure of humans to such toxins emerging from dietary sources, aquatic environments, industrial and atmospheric sources influence normal cellular physiology, which in combination with the underlying human genetic disposition influence unknown to-date pathways linked to neurodegenerative events. Over the last decades, aluminum (Al) has been linked to numerous human pathological disorders, emphatically associated with the onset of neurological diseases [1,2,3], including Alzheimer's disease. The present study targets the chemical reactivity of well-characterized Al(III) forms in a neuronal and glial cellular environment, thereby lending credence to the association of Al(III) with Alzheimer Disease etiopathology [3-5]. The selected molecular targets interacting with Al(III) are N-methyl D-aspartic acid (NMDA) and Voltage-Dependent Calcium Channels (VDCC), both of them key structures on neurocellular membranes, playing an important role in memory processes. The experimental effort attempts to assess the neurotoxic potential of Al(III) interacting with the above cellular receptors, thereby contributing to neurodegeneration in Alzheimer Disease.

Keywords: aluminum, environmental neurotoxin, cell receptors and calcium channels, Alzheimer, neurons

1. Introduction

Over the past two decades, metallotoxins (iron, copper, aluminum) have been implicated in the onset and progression of neurodegenerative processes. Albeit ill-understood, these neurotoxins have been linked to numerous neuropathological disorders including Alzheimer's Disease [6,7]. Among the specific targets – associated with hippocampal cells – are the N-methyl D-aspartic acid (NMDA) and Voltage-Dependent Calcium Channels (VDCC), stimulating receptors on neurocellular membranes linked to Ca(II) homeostasis and playing an important role in memory [8,9]. The interactions between Al(III) and the aforementioned targets are the subject of the current investigation, seeking to understand the implications of the unfolding chemistry with structure specific soluble aluminum a) being bound to low molecular mass hydroxycarboxylic acids involved in cellular processes, and b) inducing neurotoxic effects on hippocampal cells, collectively effecting neurodegeneration in Alzheimer's disease.

2. Materials and Method

In an effort to comprehend the transport of this neurotoxic metal ion from the environment to the human neurocellular machinery, ultimately ending in the brains of Alzheimer patients, exhaustive synthetic and physicochemical work was employed along with acute toxicity studies, using Ca(II) imaging techniques, on primary rat hippocampal cell cultures. Five various forms of Al (Table 1) and the inorganic Al were employed in the present study.

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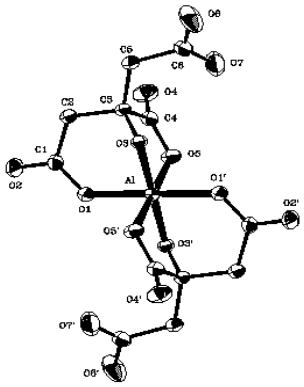
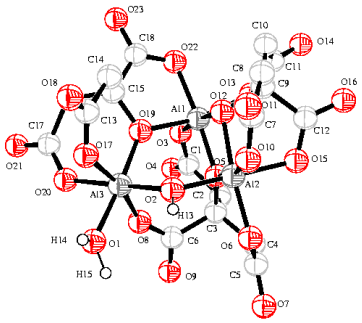
Table 1: General profile of the Al(III) species employed in the study

Compound X-ray crystal structure in the solid state	Potential species emerging in solution*
$K[Al(C_7H_{11}O_6)_3]\cdot(OH)\cdot 4H_2O$, AlQ	$[Al(C_7H_{11}O_6)_2(OH)]^0$ [10]
$(CH_6N_3)_4[Al_2(C_5H_6NPO_7)_2(OH)_2]\cdot 8H_2O$, AlNTAP	$[Al(C_5H_6NPO_7)(OH)]^{2-}$ [11]
$(NH_4)_5[Al(C_6H_4O_7)_2]\cdot 2^H_2O$, AlCit1	$[Al(C_6H_4O_7)(OH)]^{2-}$ [12]
$K_4[Al(C_6H_4O_7)(C_6H_5O_7)]\cdot 4H_2O$, AlCit2	$[Al(C_6H_5O_7)(OH)]^-$ [13]
$(NH_4)_5[Al_3(C_6H_4O_7)_3(OH)(H_2O)]\cdot(NO_3)\cdot 6H_2O$, AlCit3	$[Al_3(C_6H_4O_7)_3(OH)(H_2O)]^{4-}$[14]





$[Al(CitH_{-1})_2]^{5-}$ $[Al_3(CitH_{-1})_3(OH)(H_2O)]^{4-}$

Figure 1. The X-ray structures of the representative binary materials (bound water ligands are omitted for clarity)

All of the above species employed in the present experimental work were synthesized and physicochemically characterized according to published procedures. Characterization included analytical, spectroscopic (e.g. FT-IR, NMR) and X-ray crystal structure determination of all species. It's worth pointing out that the species employed included a) mononuclear as well as oligonuclear species, b) hydroxycarboxylate as well as carboxyphophosphonate binding substrates, and c) pH-dependent structural variants reflecting into the structural aqueous speciation of the binary Al(III)-hydroxycarboxylate and Al-carboxyphosphonate systems.

A representative set of these binary materials of well-defined physicochemical characteristics are shown in Figure 1, with the X-ray structures derived from crystallographic work pointing out the key features at the atomic level that justify the chemical reactivity of Al(III) when interacting with the target NMDA and VDCC channels on the hippocampal cells.

Key to the use of the aforementioned species in the present investigation was the perusal and subsequent correlation of the structure of theses species AlQ, AlNTAP, AlCit1, AlCit2 and AlCit3 in the solid state and in solution. To this end, the nature of the species arising in solution was determined through the available spectroscopic techniques and kinetic studies, conducted on the premise that Al(III) species are kinetically inert, thereby allowing for pertinent investigations on the NMR spectroscopic time scale.

3. Results and Discussion

The well-defined aluminum forms interact with the NMDA and VDCC channels in variable modes dictated by the nature of the metal ion and their solution properties. Calcium response varies in the two channels and depends heavily on their structure, composition and biochemical function. Short and long term exposure of the cells to aluminum defines their susceptibility to apoptosis and necrosis as evidenced by Ca(II) homeostatic variations at both the neuronal and glial cell level. The sum-up results of the current study is presented below in Table 2.

Table 2: Comparison of the effects of the Al compounds on NMDA and VDCC channels

	NMDA			**VDCC**		
Metal form	**10μM**	**100μM**	**500μM**	**10μM**	**100μM**	**500μM**
Al-S	*	***	Δ ***	**ns**	**	Δ ***
AlQ	***	***	***	***	**	**ns**
AlNTAP	***	***	***	**ns**	**ns**	***
AlCit1	***	*	***	**ns**	**ns**	**ns**
AlCit2	***	*	***	***	*	***
AlCit3	**	***	***	**ns**	**ns**	**ns**

Full and irreversible block: Δ
Post-test analyses (Dunn's): P<0.05=* (significant), P<0.01=** (highly significant), and P<0.001=*** (extremely significant).

4. Conclusion

The results unravel the diverse reactivity of neurotoxic aluminum as that is formulated by the nature of bound ligands in aqueous media, the arisen speciation thermodynamics, and portray the effects brought on by its variably structured complex forms. The interaction of the well-defined forms of aluminum with NMDA and VDCC cellular structures denote the salient features of both reactants and describe the key factors (size, hydrophilicity, hydrophobicity, charge distribution, local structure, chemical reactivity) affecting Ca(II) homeostasis and render neuronal and glial hippocampal cells variably susceptible to degenerative processes.

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