

## **PROGRESSIVE LOSS OF HIPPOCAMPAL CELLS BY EXPOSURE TO Al(III) COMPOUNDS. EMPHASIS ON ALZHEIMER DISEASE**

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### **Abstract**

*The last decades, aluminium (Al) has been linked with a numerous of human pathological disorders especially with the onset of neurological diseases as Alzheimer (Crapper, 1976), microcytic anaemia (Kerr, 1988), Pick. Until today, the potential (neuro)toxicity of aluminum (Al) and its correlation with the Alzheimer Disease aetiopathology (Fasma, 1994; Vyas, 1995; Clauberg, 1993) has been under debate. In an effort to comprehend the role of that metal ion in disease, we investigated the potential biological activity of well-characterized Al(III) forms in neuronal and glial cellular environment. The undertaken effort constitutes a challenge, because of the neurotoxic potential of the metal and the epidemiological evidence linking aluminum to Alzheimer Disease.*

**Keywords:** *aluminum, toxicity, neurodegeneration, structural speciation, Alzheimer, neurons, glial cells*

### **Introduction**

Alzheimer Disease (A.D.) is a central nervous system neurodegenerative disease (Berne, 1996), which is characterized by the presence of senile plaques and neurofibrillary tangles. The involved genetic and environmental factors in the development of A.D. (Platt, 2006) include various mutations on Amyloid Precursor Protein (APP) and Presenilin 1,2 genes, and numerous metallotoxins like aluminum (Al(III)).

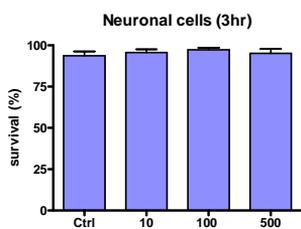
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There is evidence linking aluminum with Alzheimer's Disease that includes: a) an elevated Al(III) concentration in bulk brain samples and in neurofibrillary tangles as well as senile plaques, b) many pathological and clinical aspects, in experimental animals, similar to those of AD that can be produced, depending on factors such as Al(III) dose, route of exposure, and type of Al(III) compound, and c) the fact that more than 100 different toxic actions of Al(III) have been identified at the molecular and cellular level, many of which occur at Al(III) concentrations, which are toxic to the human brain. Elevated intracellular levels of Al(III) have pleiotropic effects such as disruption of cytoskeletal system, inhibition of proteolysis, and deregulation of gene expression. Al(III), upon entering the nucleus, binds irreversibly to negatively charged groups of chromatin, and inhibits nucleic acid synthesis of DNA, hence resulting in serious cell damage, which may cause AD (Flaten, 2001).

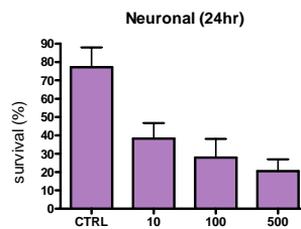
The investigation of the potential biological activity of well characterized Al(III) forms in neuronal and glial cellular environment consists a challenge, because of the neurotoxic potentiality of the metal and the evidence linking Aluminum to Alzheimer Disease.

## **Experimental**

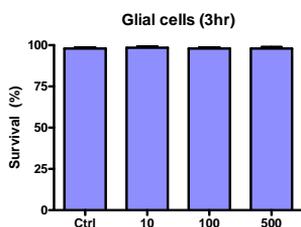
In the context of this research, neuronal and glial cell cultures of neonate rat Prague-Dawley were exposed to two novel Al(III) compounds, namely, aluminium quinate ( $K_4[Al(C_6H_4O_7)(C_6H_5O_7)] \cdot 4H_2O$ ) and aluminium citrate ( $K[Al(C_7H_{11}O_6)_3](OH) \cdot 5H_2O$ ). The concentrations were i) 10  $\mu$ M, ii) 100  $\mu$ M or iii) 500  $\mu$ M in HEPES Buffer Solution for an incubation of 30 minutes or in full medium MEM for an incubation of 24 hours. After this procedure, the cells were stained a) first with a propidium iodide (PI) solution, which selectively labels nucleic acid in necrotic cells due to its inability to penetrate the membrane of healthy cells, and b) then with 4',6-diamidino-2-phenylindole (DAPI), which determines the total number of cells. The image acquisition was carried out with the laser-scanning confocal imaging system microscope to find out the percentage of survival/dead neuronal or glial cells. After statistical analysis, we found the below results (*diagrams 1, 2, 3, 4*).



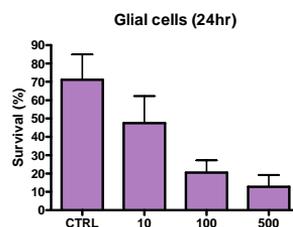
1



2



3



4

## Conclusions

After statistical analysis, we found that:

- ❖ Longer exposition time of both aluminium compounds causes more catastrophic effects on neuronal and glial cell lines ( *see diagrams 2 and 4* )
- ❖ The loss of the hippocampal cells caused by the metal ion is directly linked with the kind of the ligands such as tricarboxylic citric acid ( $C_7H_{11}O_6$ ) and  $\alpha$ -hydro-carboxylic quinic acid ( $C_6H_5O_7$ ), which bind the metallotoxins and can determine the interaction with biological targets at the molecular level and its neurotoxic effects.
- ❖ Dose-response relationships were found at 10, 100 and 500  $\mu M$  in long term MEM treatment conditions. Higher concentrations of Al(III) lead to greater loss of neuronal and glial cells ( *see diagrams 2 and 4* ).

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- ❖ No significant loss of neuronal and glial cells was observed under short term HBS treatment conditions ( *see diagrams 1 and 3*)

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