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Neuroprotective effects of chelator agents toward aluminium and Aβ amyloid peptide interactions in hippocampal cells

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Abstract

Alzheimer's disease (AD), as the most common type of dementia, is a neurodegenerative disease characterized by progressive cognitive deterioration [**1**], together with declining activities of daily living, neuropsychiatric symptoms or behavioral changes and progressive loss of memory. Aβ is generated from the Amyloid Precursor Protein (APP), a molecule implicated in neurotrophic actions [**2,3**] and brain repair from nerve injuries, thus maintaining healthy brain tissues and regulating neural synaptic activity, plasticity and memory [**4**]. Aluminum, as a metallotoxin, has also been found to play a role in the precipitation and cytotoxicity of APP-originating amyloid Aβ peptide [**5**] in Alzheimer's disease. 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 investigation of the potential biological activity of well-characterized Al(III) forms in cellular environment constitutes a challenge, because of the neurotoxic potential of the metal interacting with the cellular peptide and the epidemiological evidence linking aluminum and Beta amyloid to Alzheimer Disease.

Keywords: Aluminum, Aβ(1-40) amyloid peptide, chelator agents, neurodegeneration, Alzheimer, neurons, glial cells

1. Introduction

Abundance of studies on discrete risk factors Aβ(1-40) amyloid peptide and aluminum have been reported over the years, inquiring into their toxicity in the brains of Alzheimer's disease patients [**5,6**]. In the current *in vitro* study, the long-term toxicity behavior of Aβ(1-40) and its potential correlation with inorganic and well-defined aluminum complexes was investigated in primary rat hippocampal cultures. Moreover, experiments with the aforementioned factors were conducted in presence of protective chelator agents (clioquinol (Clio), desferrioxamine (DFO) and the physiological quinic acid (QA)) in order to investigate the interactions among these diverse factors.

2. Materials and methods

In the course of this research, neuronal and glial cell cultures of neonate Sprague-Dawley rats were used for the experiment. Short and long term incubations of the cells were implemented in presence of Al(III) compounds ($AlCl_3$ and Al-quinate $K[Al(C_7H_{11}O_6)_3]\cdot(OH)\cdot 4H_2O$) or combination of Al(III) with Aβ(1-40), respectively, at the appropriate concentrations. Furthermore, chelator agents (clioquinol (Clio), desferrioxamine (DFO) and the physiological quinic acid (QA)) were applied to the above conditions, separately. Cell staining and Image acquisition were made allowing survival cell assessment.

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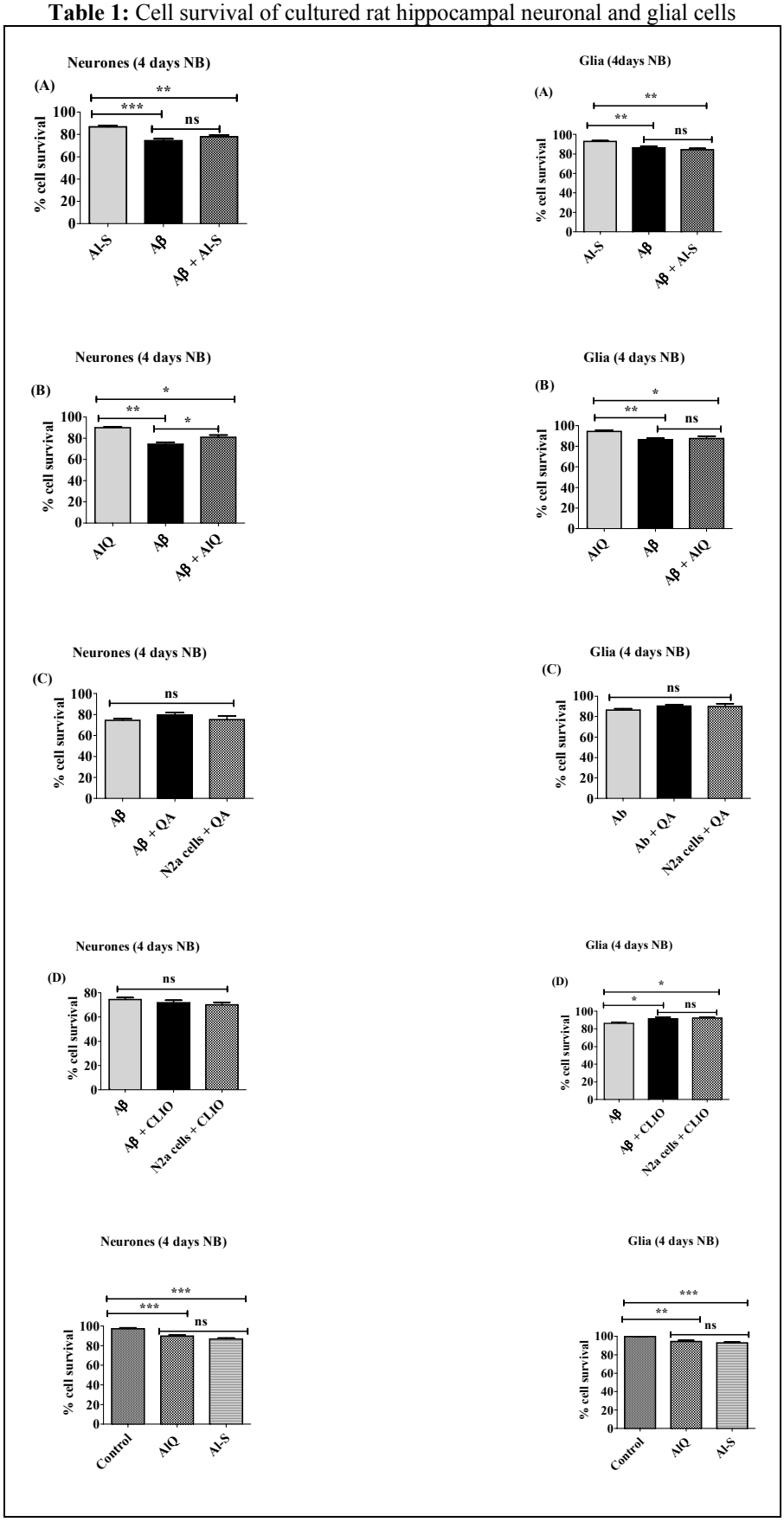
Table 1: Cell survival of cultured rat hippocampal neuronal and glial cells



The compounds concentrations used were after 4 d incubations with AlQ (50 μM), Al-S (50 μM), Aβ (1.11 ρM), Aβ (1.11 ρM) + AlQ (50 μM), Aβ (1.11 ρM) + Al-S (50 μM), Aβ (1.11 ρM) + QA (1.5 mM) and Aβ (1.11 ρM) + CLIO (100 μM) in NB and medium from N2a cells incubated with QA (1.5 mM) and CLIO (100 μM); Statistical significance is indicated relative to control cultures treated with neurobasal medium only (*P<0.05, **P<0.01, ***P<0.001).

3. Results and Discussion

The experimental data indicate that diminution of the survival rate of neuronal and glial cells due to Al(III) toxicity - $AlCl_3$ and Al-quinate $K[Al(C_7H_{11}O_6)_3]\cdot(OH)\cdot 4H_2O$ - was dependent on exposure time, the nature of the ligand bound to the metal and cell susceptibility. The collective data suggest that the Aβ peptide and well-defined forms of aluminum likely follow different biotoxic molecular pathways of action on hippocampal cells *in vitro*, with no apparent synergistic effects. The protective effects of the chelator agents Clio, DFO and QA against Al(III) toxicity were explored, showing statistically significant positive results. Of the three employed chelator agents *in vitro*, naturally occurring QA showed for the first time well-defined neuroprotective properties comparable to those of Clio and DFO, thus presenting itself as a challenge in future studies aimed at the development of structure specific anti-degenerative pharmaceuticals in Alzheimer's disease.

4. Conclusion

Aβ toxicity is variably a) regulated through interactions with soluble complex forms of Al(III) interacting with it prior to reactivity with neurons, and b) modulated by the nature of Al(III) interacting with neurons prior to any toxic chemical reactivity exerted by Aβ.

To this end, further work is needed to clarify the mechanism of action of Aβ. Furthermore, a well-defined protection profile remains to be investigated for QA when the latter is applied to neurons and glia exposed to both Al(III) and Aβ risk factors.

Its natural origin linked to the chemistry of cellular physiology is in line with the protective results exhibited in this study and predisposes for in-depth details of its molecular interactions providing for neuronal protection in sensitive loci.

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