Biochemical and Molecular Biological Insights into Aluminum Toxicity in Biology and Medicine

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Abstract: It was shown that the rate of excretion of aluminum in the urine was assumed to have a limiting value. Therefore, an excess intake of aluminum indicated that the aluminum content in the body remained high for several days after the absorption of aluminum from the intestine. Accumulation of aluminum in the body has been linked to disease conditions. The toxic effects of aluminum to neuronal cells were examined to show apoptotic cell death via endoplasmic reticulum stress, implicating an influence of aluminum on the gene expression. Also, it was shown that astrocyte-neuron interaction was important in the process of toxic effects in the central nervous system. In addition, renin was the only positively identified up-regulated gene in kidneys determined by DNA sequencing. The up-regulation of renin was confirmed by RT-PCR and Western blotting experiments in the dose dependent treatments and the time course observation in mice. The up-regulation of the renin expression by aluminum is a strong indication of the influence of aluminum on the renin-angiotensin-aldosterone-system, resulting in the induction of essential hypertension.

Key-words: aluminum, urinary excretion, astrocytes, neuron-astrocyte interaction, neurodegenerative disease, renin, essential hypertension

1. Introduction

Aluminum is the third abundant element and the most abundant metal in the earth's crust, therefore exposure to aluminum is inevitable in daily life. Aluminum is not an essential element but is rather toxic and the need to protect themselves from aluminum toxicity is crucial for living organisms. The kidneys play a major role in preventing the harmful accumulation of aluminum, excreting aluminum from the body. Diverse studies have been conducted on metabolism, excretion and the nephrotoxic effect of aluminum [1]. Different mechanisms of renal excretion of aluminum such as glomerular filtration, tubular reabsorption of filtered aluminum and secretion in distal nephron and excretion in the distal tubules have been suggested. However, the regulation mechanism of aluminum excretion has not been clear.

Aluminum is also among the well-known elements toxic to the central nervous system (CNS); especially, it has been implicated as a cause of neurodegenerative diseases such as dialysis encephalopathy, amyotrophic lateral sclerosis and Parkinsonisms dementia on the Kii peninsula and in Guam. The relation between Alzheimer's disease (AD) and aluminum is still controversial in spite of

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much research work and debate over a long period. The existing data for the hypothesis of aluminum as a cofactor in the etiopathogenesis of AD remain mostly at the phenomenological level, partly owing to the intricate biochemistry of Al^{3+} . Astroglial cells play important roles in the CNS by maintaining nerve cells; providing metabolic and trophic support, contributing to functional blood-brain-barrier, secreting specific metabolites at the demand of neurons, protecting neurons against foreign toxic substances, contributing to local modulation of synaptic efficacy at excitatory inputs by controlling glutamate clearance and so many other newly reported functions that have never been attributed to astrocytes.

Recently it has been implicated that the risk of hypertension increases in the aluminum exposure in manufacturing employees [2]. But there has been no report on the effect of aluminum on renal gene expression. The pathological influences of aluminum may appear chronically, but the gene expression may start to be altered in an early time of the exposure to aluminum.

2. Aluminum stays in a long period in blood after taking aluminum containing drugs

The daily intake and excretion of aluminum in urine were measured for volunteers. Total intakes of aluminum from ordinary foods with and without aluminum hydroxide medication were 305.9 and 5.9 mg/day, respectively. The overall apparent absorption rate of aluminum hydroxide antacid was 0.003% and the apparent biological half-time is 7.4±1.4h. However, in the case of aluminum glycinate apparent absorption rate was 0.38 ±0.29%, which was much higher than the case of aluminum hydroxide. The relationship between aluminum concentration in urine (ng/ml) and the rate of urine production (ml/min) after taking an antacid revealed a hyperbolic curve by non-linear least square calculation. These results of high excretion of aluminum indicated that the aluminum content of the body remained very high for several days after the absorption of aluminum from the intestine [1, 3, 4].

3. Neonates are highly susceptible to aluminum poisoning

Aluminum toxicity among infants and children has been cited in the medical literature for several decades describing serious central nervous system, bone and liver damage, and anemia. We reported an extremely high content of aluminum in the brain and a high concentration of aluminum in the serum were observed in the two siblings with CNS calcification, tubular acidosis and microcytic anemia who have normal renal function. These data suggest that the mechanism to protect against transportation of aluminum through the blood-brain-barrier was not functioning adequately. In addition, the mechanism of urinary excretion of aluminum may have been impaired [5].

4. Aluminum induces apoptosis not by mitochodria but ER stress in astrocytes

Gene expression analysis revealed that Ire1β was up-regulated in astrocytes exposed to aluminum while Ire1α was up-regulated by tunicamycin. Exposure to aluminum glycinate, in contrast to tunicamycin, seemed to down-regulate mRNA expression of many genes, including the ER resident molecular chaperone BiP/Grp78 and Ca-binding chaperones (calnexin and calreticulin), as well as stanniocalcin2 and OASIS. The down-regulation or non-activation of the molecular

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chaperons, whose expressions are known to be protective by increasing protein folding, may spell doom for the adaptive response. Exposure to aluminum did not have any significant effects on the expression of Bax and Bcl2 in astrocytes. Aluminum may induce apoptosis in astrocytes via ER stress by impairing the protein-folding machinery [6, 7].

5. Astrocyte-neuron interaction is disrupted by aluminum

Aluminum may be taken up as amino acid complex by astrocytes. Citrate has been identified as a major tricarboxylic acid (TCA) cycle constituent preferentially released by astrocytes. We undertook the study to examine further the nature of metabolic compartmentation in central nervous system tissues using ^{13}C-labeled glucose and to provide new information on the influence of aluminum on the metabolic interaction between neurons and astrocytes. Metabolites released into the culture medium from astrocytes and neuron-astrocyte co-culture, as well as the perchloric acid extracts of the cells were analyzed using 2D ^{1}H and ^{13}C NMR spectroscopy. Astrocytes released citrate into the culture medium and the released citrate was consumed by neurons in co-culture. Citrate release by astrocytes was blocked in the presence of aluminum, with progressive accumulation of citrate within the cells. We propose that citrate supply is a more efficient energy source than lactate for neurons to produce ATP, especially in the hypoglycemic state on account of it being a direct component of the TCA cycle. Astrocytes may be the cellular compartment for aluminum accumulation as a citrate complex in the brain [8, 9].

6. Neuronal cells *in vitro* suffer seriously from aluminum to reveal neurodegenerative symptoms

Aluminum accelerates production of the presenilin2 (PS2) and HMGA1a like in a sporadic AD brain. Oxidative stress is a major risk factor for AD and other neurodegenerative disorders. The aberrant splicing isoform (PS2V) generated by skipping exon5 of the PS2 gene is a diagnostic feature of sporadic AD. We demonstrated that exposure to aluminum accelerated PS2V production induced by hypoxia. This acceleration of the production of PS2V to hypoxia was caused by chronic aluminum exposure, but was not related to the intracellular content of aluminum. HMGA1a is a mediator of PS2V production, and it was induced by aluminum as well as by hypoxia. Induction of HMGA1a was increased by chronic exposure to aluminum, and a nuclear extract containing HMGA1a bound to a specific sequence on exon5 of PS2 pre-mRNA. These results suggest that exposure to aluminum can accelerate and enhance PS2V generation, and that hypoxia plus chronic exposure to aluminum may promote the development of AD [10].

We investigated whether aluminum might be involved in neurofibrillary tangles formation by using an in vitro tau aggregation paradigm, a tau-overexpressing neuronal cell line (N2a), and a tau-overexpressing mouse model. Although aluminum induced tau aggregation in a heparin-induced tau assembly assay, these aggregates were neither thioflavin T positive nor did they resemble tau fibrils seen in human AD brains [11].

7. Aluminum induces up-regulation of renin gene in kidneys

The effect of aluminum on the kidney was further investigated by the study of gene expression in

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mice. Analyses of gene expression revealed that eight genes were up-regulated while five genes were down-regulated. After a single dose of aluminum, an up-regulation of renin gene was found by DNA sequencing of the products of differential display analysis. The up-regulation of renin (Ren1) was confirmed by RT-PCR and Western blotting experiments in the dose dependent treatments and the time course observation after aluminum citrate injection. The up-regulation of the renin expression by aluminum is a strong indication of the influence of aluminum on the renin–angiotensin–aldosterone system, resulting in possible induction of essential hypertension [1].

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