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Aluminum hemotoxicity mechanisms

Both aluminum and its salts are commonly used by people. Aluminum plays an important role in the production of kitchen utensils, packaging and other tools. Aluminum salts have been used in pharmaceutical and cosmetic industries. Aluminum sulfate is used to purify turbid drinking water from organic components. Aluminum salts are added to fodders and foodstuffs because of their loosening properties. They also stabilize pH and prevent caking. Aluminum salts are components of drugs used in stomach and duodenum ulcer treatment, buffered painkillers and drugs used in hyperphosphatemia treatment (2).

Such a widespread use of aluminum was enhanced by the belief that it is not toxic and is quickly excreted from the body with urine. It turned out, however, that this element has a negative impact on human health. Post-dialysis encephalopathy of patients with kidney malfunctioning was ascribed to the presence of aluminum in dialysis fluid. Therefore, the content of aluminum in dialysis fluid is limited now. Alfrey et al. (1) state that water used in fluid preparation should not contain more than 10 mg Al/l. Currently it is suggested that Al level should not exceed 5 mg Al/l.

Aluminum cumulating in brain tissue is claimed to play a role in developing neurological disorders (10). This element affects bones as well as it causes disturbances in phosphorus and calcium levels, which is demonstrated chiefly by osteomalatia. Aluminium accumulation in the liver leads to cholestasis and disturbances of liver microsomes. This element causes numerous changes in peripheral blood and hemogenic system. It also causes normo- or microcytary anemia as it disturbs maturing of erythroblastic series cells and heme biosynthesis; it decreases osmotic resistance of red blood cells. Aluminum inhibits defensive mechanisms connected with white blood cells and macrophages.

A number of processes, namely aluminum's hemolytic activity, blood cells' shorter lifetime or disturbed erythropoesis process, are responsible for hematological changes. Aluminum's hemolytic activity is connected with changes in cell membrane of red blood cells. Rabbit erythrocytes in hydrolytically stable lipophilic aqueous $Al(acac)_3$ solution assume the form of echinoacanthocytes (5). Changes in blood cell morphology are connected with changes in membrane fluidity. This assumption was confirmed by research in human erythrocytes exposed to aluminum hydroxide in micromolar concentration at pH 7.4 (13). It is commonly known that this element acts as a pro-oxidant. Similarly to other xenobiotics, it generates free oxygen radicals that begin peroxidation of lipids which contain non-saturated fatty acids. It enhances the appearance of numerous organic free radicals, dienes and aldehydes in a cell. Malone dialdehyde (MDA), one of these compounds, while reacting with membrane protein amino acids forms Schiff's base-type bonds. It leads to the reduction in membrane fluidity and hence decreases its ability to reshape which, consequently, may result in serious defects (15). Changes in cell membranes lead to decreased activity of membrane ATP-ases. Adenylates accumulate inside a cell and the speed of ATP changing into ADP is lowered. This reduces the amount of energy necessary to maintain membrane

integrity and leads to dysfunctions and blood cell hemolysis, especially when aluminum influence is long-lasting. Moreover, it was shown that Al forms bimolecular adducts with phosphatide groups. Formation of stable bonds between Al and membrane phospholipds can have a huge influence on supermolecular ordering of membrane bi-layer and hence influences its integrity (15).

Although there are numerous antioxidants protecting organisms against free reagents, in case of aluminum intoxication the activity of a number of components of anti-oxidation system is inhibited. It has been proved that this element, both *in vivo* and *in vitro*, reduces the activity of superoxide dismutase (SOD), peroxidase (PX), catalase (CAT) and glutation peroxidase (GPX) (11), as well as of L-ascorbine acid (14). The decrease in the level of this acid under the influence of aluminum is connected with the influence of this element on the activity of L-gulonoacton oxidase, an enzyme that catalyzes the reactions of transforming L-gulonoacton into 2-keto-L-gulonolacton, a direct precursor of L-ascorbine acid (Fig. 1). Aluminum activating glucose-6-phosphate dehydrogenase and glutation reductase in bone marrow and peripheral blood erythrocytes can lead to accelerated blood hemolysis (14).

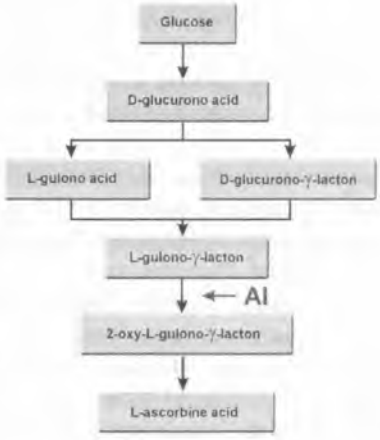

Fig. 1. Aluminium effect on L-ascorbine acid biosynthesis

The reduced number of red blood cells may not only result from aluminum's hemolytic activity, but also from a shorter blood cell life time. Cells with membranes whose ability to reshape has been reduced are not kept in reticular-endothelial system and hence they are eliminated from blood circulation system (7).

The decrease in red blood cell number is accompanied by a higher level of reticulocytes in peripheral blood, which to some extent compensates aluminum's hemolytic activity. It should be noticed, however, that the increased level of these blood cells does not compensate for the deficit of erythrocytes caused by their decomposition. According to Z a m a n et al. (14), it proves that aluminum inhibits erythropoesis and blood cell maturing. The authors confirmed their assumptions stating that the above-mentioned changes in peripheral blood are accompanied by a lowered level of proerythroblasts and all three types of erythroblasts. According to them, the influence of aluminum on blood cell maturing is connected with this element forming a very stable complex with ATP. The stability constant of this complex is 4,000 greater than of Mg-ATP complex. Therefore, 0.2 μM Al^{3+} can compete with 1 mM Mg^{2+} in forming bonds with ATP (6).

Reticulocytes, i.e. the last immature form in erythropoetic series, contain non-lysosome ATP-dependent system eliminating some proteins while maturing and transforming into mature red blood cells. Hence, an insufficient ATP level might inhibit this system and hinder erythrocyte maturing at this very level of erythropoesis (14).

Disturbances in heme biosynthesis are another change in red blood cell system caused by aluminum. It was shown that both aluminum chloride and nitrate in 10–20 μM doses impede ^{50}Fe inclusion into heme in marrow of rats (14).

Aluminum influences the efficiency of enzymes participating in heme biosynthesis (14). The activity of this element involves mainly delta-amino-levulinic acid dehydratase (ALA-D), an enzyme catalyzing condensation of two molecules of delta-amino levulinic acid into a molecule of porphobilinogen. It distorts the formation of uroporphyrin III and coproporphyrin III, and consequently protoporphyrin III, which is a heme precursor (Fig. 2).

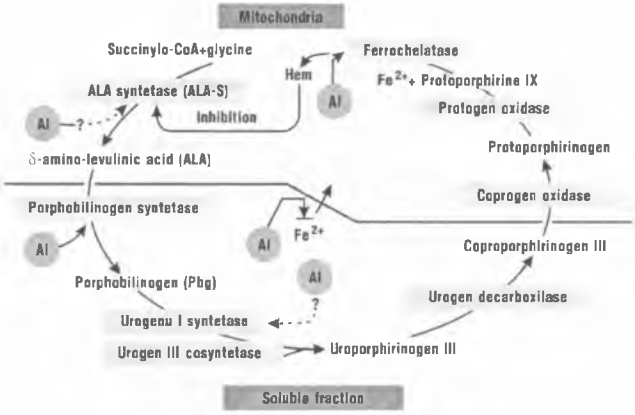

Fig. 2. Aluminium effect on heme biosynthesis

ALA-D catalytical activity is much lower in case of people undergoing hemodialyses (4). Aluminum salts markedly reduce the activity of this enzyme in rats as well (9). ALA-D reduced activity is caused by Al^{3+} ions being attached to thiol groups present in various enzymatic reactions (14).

Aluminum exerts a significant influence on oxygen transport by hemoglobin. As we know, red blood cells are characterized by a specific metabolic route, so-called Rapoport-Luebering shunt, which constitutes a glycolysis branch at the level of 1,3-diphosphoglyceric acid (1,3-DPG) – Figure 3. In this cycle 2,3-diphosphoglyceric acid (2,3-DPG) is formed from 1,3 DPG by means of phosphoglyce--romutase enzyme. 2,3-DPG regulates hemoglobin affinity to oxygen. 2,3-DPG concentration depends not only on phosphoglyceromutase and 2,3- diphosphoglycerate phosphatase, but also on the activity of phosphofructokinase. The increased activity of this enzyme accelerates glycolysis and leads to increased 1,3-DPG concentration. 1,3-DPG is phosphoglyceromutase substrate. 2,3-DPG degradation, in turn, is caused by 2,3-diphosphoglycerate phosphatase with 3-phosphoglycerate and non-organic phosphate being created (12). Aluminum enhances 2,3-DPG hydrolysis and inhibits glycolysis by joining glucoso-6-phosphatic dehydrogenase –SH groups and reducing its activity (14).

Research on animals showed that aluminum intoxication leads to the increase in white blood cells and changes in leukogram leading to neutrophilia and lymphopenia, whose intensity depends on the dose and intoxication time (7, 8). A similar reaction of leukocyte system can be observed as a response to various stress factors. It seems, however, that aluminum doses administered by the above-mentioned researchers were too low to be regarded as a stress factor. The proper stress was caused by red blood cell hemolysis triggered by intoxication.

Zaman et al. (14) associate the decreased number of white blood cells with aluminum's toxic influence on T lymphocytes as these blood cells exhibit a particularly high affinity to Al^{3+} ions. It was

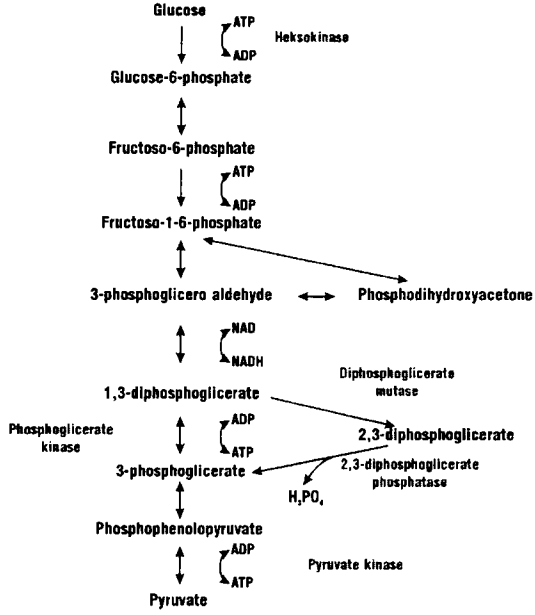

Fig. 3. Glycolysis in red blood cell

discovered that $Al(OH)_3$ intraperitoneal injections in mice cause a very huge reduction of mitogenic PAH effect for T lymphocytes and lyposaccharide (LPS) for B lymphocytes. It inhibits lymphocyte blastic transformation and consequently causes the reduction of hormonal and cellular resistance (14).

It is known that body resistance is reduced in case of iron deficits. Its deficits result in white blood cells losing their ability of blastic transformation. During this process, blood cells need more iron, which is transported by means of transferrin. Due to their physicochemical similarity, aluminum, after overcoming the barrier of mucosa, competes with iron to take place in a bond with transferrin. It might be one of mechanisms inhibiting defensive functions of white blood cells.

The reduction of monocyte number observed in experiments on animals may be explained by the fact that aluminum together with low-molecular proteins is absorbed by peripheral macrophages and reticular-endothelial system, which leads to the disintegration of a cell undergoing phagocytosis. Lower level of monocytes might also cause hindering of lymphocytes' defensive functions. It was demonstrated that in order for the immunological response to be proper, a specific number of white blood cells must be proportional to macrophages. The latter excrete special substances – monokine, which can be both activating and suppressing. Lymphocyte activating factor (LAF), which stimulates DNA synthesis and increases T lymphocyte response to mitogen activity, is the best known activating factor (3).

Aluminum's immuno-inhibitory activity can also be related to phagocytosis deficits. Both granulocytes and monocytes present in blood of rats intoxicated with aluminum exhibited reduced phagocytic activity and lower levels of the following enzymes: glucoso-6-phosphatic dehydrogenase, glutathion peroxidase and myeloperoxidase. These enzymes are necessary to maintain all phagocyte anti-bacteria properties. As might be expected, the reduced level of L-ascorbine acid, indispensable for the proper course of phagocytosis can also be accounted for by reduced phagocytic activity (14).

On the basis of the above-mentioned data it appears that aluminium is an environmental factor that plays an important role in some hemogenic system disturbances. It seems justified that in case of

anemia with simultaneous disturbances of heme biosynthesis and iron metabolism the level of this element in blood should be determined.

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SUMMARY

Both aluminum and its salts are commonly used by people. Aluminum salts are components of drugs. Such a widespread use of aluminum was enhanced by the belief that it is not toxic and is quickly excreted from the body with urine. It turned out, however, that this element has a negative impact on human health. Post-dialysis encephalopathy of patients with kidney malfunctioning was ascribed to the presence of aluminum in dialysis fluid. Aluminum cumulating in brain tissue is claimed to play a role in developing neurological disorders. This element affects bones as well as it causes disturbances in phosphorus and calcium levels, which is demonstrated chiefly by osteomalatia. Aluminium accumulation in the liver leads to cholestasis. This element causes numerous changes in peripheral blood and hemogenic system. It also causes normo- or microcytary anemia as it disturbs maturing of erythroblastic series cells and heme biosynthesis; it decreases osmotic resistance of red

blood cells. Aluminum inhibits defensive mechanisms connected with white blood cells and macrophages. A number of processes, namely aluminum's hemolytic activity, blood cells' shorter lifetime or disturbed erythropoiesis process, are responsible for hematological changes.

Mechanizmy hemotoksyczności glinu

Zarówno glin, jak i jego sole są powszechnie stosowane w codziennym życiu człowieka. Stanowią one również składnik wielu leków. Tak szerokie zastosowanie glinu było oparte na przekonaniu, że nie jest on toksyczny dla organizmu, z którego jest szybko wydalany wraz z moczem. Okazało się jednak, że pierwiastek ten ma szkodliwy wpływ na zdrowie człowieka. Powiązano występowanie encefalopatii podializacyjnej u chorych z niewydolnością nerek z obecnością glinu w płynie dializacyjnym. Kumulacji tego pierwiastka w tkance mózgowej przypisuje się rolę w powstawaniu wielu zaburzeń neurologicznych. Glin działa też na układ kostny, powodując zaburzenia w gospodarce fosforanowej i wapniowej, przejawiające się głównie osteomalacją. Jego kumulacja w wątrobie prowadzi do cholestazy. Pierwiastek ten wywołuje też szereg zmian we krwi obwodowej i układzie krwiotwórczym. Jest przyczyną anemii o charakterze normo- lub mikrocytarnym, zaburza bowiem dojrzewanie komórek układu erytroblastycznego i biosyntezę hemu, obniża oporność osmotyczną erytrocytów. Glin upośledza też mechanizmy obronne organizmu, związane z limfocytami i makrofagami. U podstaw zmian hematologicznych leży kilka mechanizmów: hemolityczne działanie glinu, skrócenie czasu przeżycia krwinek, zaburzenia procesu erytropoezy.