Review article

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PATHOPHYSIOLOGICAL MECHANISMS OF ALUMINIUM TOXICITY

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Aluminium forms about 8% of the earth's crust. It is most commonly found as bauxite ore, which is used for extraction of this metal. Aluminium has a high reactivity and forms compounds such as aluminium oxide, aluminium hydroxide, and potassium aluminium sulfate. Exposure of these compounds to oxidants leads to the formation of a superficial coating of aluminium oxide, which is highly resistant to corrosion and insoluble in water. However, acid rains have allowed the dissolution of these compounds and the entry of aluminium into biological systems. It can enter in human body through water, food, drugs, and inhalation of polluted air.

Once when accumulates in the body aluminium exhibits toxic effects on different organ systems: central nervous, respiratory, skeletal, hematopoietic, reproductive, digestive (liver), and integumentary system. Toxic systemic effects of aluminium are first observed in patients with kidney failure treated with medicines containing aluminium compounds which manifest as: dialysis encephalopathy syndrome, osteomalacia with osteodystrophy and microcytic anaemia.

Aluminium is on the top of a surprisingly short list of neurotoxic inorganic elements and their compounds. It is linked with development of neurodegenerative diseases, including autism, attention deficit disorders, amyotrophic lateral sclerosis, Alzheimer's disease, dementia, Gulf war syndrome, and Parkinsonism. Clinical and experimental studies suggest several possible mechanisms of toxic aluminium action on cells. Those are: increased production of oxidative stress, alteration of membrane function, disruption of intracellular signaling, and alteration or inhibition of enzyme functions.

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Introduction

Aluminium (Al) is a silvery-white, lightweight, ductile, malleable and non-magnetic metal. It has atomic number 13 and belongs to boron group of the periodic table of the elements. Al forms about 8% of the earth's crust. Native aluminium is extremely rarely found in nature. It is most commonly found as bauxite ore, which is used for extraction of this metal. Aluminium has a high reactivity and forms compounds such as aluminium oxide, aluminium hydroxide, and potassium aluminium sulfate. Exposure of Al to water, oxygen or other oxidants leads to the formation of a superficial coating of aluminium oxide, which is highly resistant to corrosion. Aluminium oxide is insoluble in water, but it is soluble in mineral acids and strong alkalis. The concentration of dissolved Al^{3+} is low in surface and subsoil waters, because Al minerals are insoluble at neutral pH. Rain-borne acidification and the use of acidifying fertilizers increase the concentration of soluble Al^{3+} in soil and waters (1-3). The result of soil pollution is an increase in concentration of aluminium in cultivated plants. This is one of the ways how aluminium may enter in food chain. It was believed that aluminium is harmless to environment, but it is shown that it is toxic to plants and animals (1-3).

Aluminium is widely used in metal alloy production, as a construction material in automotive and aviation industry, electrical industry, as solid fuel rocket propellent, for manufacture of explosives and fireworks. It is also used for the production of cooking utensils and dishes, for food packaging (cans, containers, foils), and as food additives (4, 5).

Mineral compounds of aluminium of natural origin (beonite and zeolite) are used to purify drinking water as coagulants in order to reduce the level of organic matter, color, cloudiness and microorganisms (4-6). Aluminium is also used in pharmacy, medicine, cosmetics and dentistry (antacids, astringents, antiperspirants, dental crowns and dentures) (5).

Aluminium can enter in human body through water, food, drugs, and inhalation of polluted air (5-7). Aluminium is a non-essential element which is not found in large quantities in human body. The total human body content of aluminium may range from 50-150 mg, with an average of about 65 mg. Daily intake of aluminium may range from 10-110 mg (8). It is characterized by low intestinal absorption, slow tissue uptake and rapid urinary excretion. Absorption of Al in the digestive tract is estimated to be less than 1%. It is influenced by solubility of Al compounds and enhanced with increased gastric acidity, presence of organic acids (ascorbic, citric) and lack of Fe and Ca in the diet. The accumulation of Al is reported in patients treated with medicines containing Al compounds (antacids, aluminium in dialysis fluid) in renal failure (8). About half of body content is found in the skeleton, one quarter in the lungs and the rest is in brain, kidneys, liver, spleen and thyroid. Aluminium may pass both blood-brain and placental barrier. It is not recognized that Al^{3+} has some function in living organisms and it is regarded as biologically inert (9, 10). Aluminium when accumulate in human body exhibits toxic effects on different organ systems: central nervous, respiratory, skeletal, hematopoietic, reproductive, digestive (liver), and integumentary system.

Effects of aluminium on central nervous system

Aluminium is on the top of a surprisingly short list of neurotoxic inorganic elements and their compounds. It is linked with development of neurodegenerative diseases, including autism, attention deficit disorder, amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), dementia, Gulf war syndrome and parkinsonism (7, 11-17).

Aluminium is accused to develop neurotoxicity through oxidative stress, cell mediated toxicity, apoptosis, inflammatory events in the brain, glutamate toxicity, effects on calcium homeostasis, gene expression, aluminium induced neurofibrillary tangle (NFT) formation and irreversible blockade of ion channels by beta-amyloid (11, 18). Neurotoxicity of aluminium salts has been reported in numerous animal studies. Exposition to excessive intake of aluminium causes learning and memory disorders in rats due to deposition of Aβ in the hippocampus and cortex. Al-induced neurophysical and neurobehavioral pathological changes similar to AD were registered in animals (19, 20). Chronic exposition of rats to high-dose $AlCl_3$ injections over a prolonged period can reduce locomotor and cognitive functions in rats as well as reduced body weight gain which may be a sign of systemic toxicity (21).

A number of clinical studies have shown that exposure to aluminium in dialysis fluid in patients with kidney failure resulted with encephalopathy. Aluminium induced encephalopathy due to bladder irrigation with 1% alum in patient with kidney failure is also reported (22). People in Camelford (south west of England) were exposed to the drinking water contaminated with 20 tonnes of aluminium sulphate in July 1988. They had considerable damages of cerebral function, which were not related to anxiety (23). A mild form of encephalopathy was registered in 64 former aluminium dust-exposed foundry workers in Italy. It was characterized by mild intellectual deficit, loss of muscle control, tremor, and spinocerebellar degeneration (24).

Aluminium levels were assessed in 118 patients with neurodegenerative diseases: multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD) as well as in 73 healthy subjects. MS was diagnosed in 85.6% of total neurodegenerative diseases (ND). Al was present in 44.8% of cases comprehensive of ND and healthy patients. Al level was significantly higher in patients with neurodegenerative diseases than in healthy subjects. Calcium disodium ethylene diaminetetra acetic acid (EDTA) chelation treatment reduced Al burden in patients with neurodegenerative diseases and ameliorated their clinical conditions (25).

Macrophagic myofasciitis was registered after intramuscular injections of Al-containing vaccines in patients (5). It was characterized by persistence of aluminium hydroxide within macrophages at the site of immunization, muscle lesions, arthromyalgias, chronic fatigue, and cognitive impairment (both visual and verbal memory deficit; including attention deficit) (26).

Aluminium salts (aluminium hydroxide, aluminium phosphate, and aluminium potassium sulfate) have been used in vaccines over eight decades. Even though it has been reported that these salts used as adjuvants can cause severe local reactions (erythema, subcutaneous nodules and contact hypersensitivity) they are still in use, because they enhance antigenicity of some vaccines (as diphtheria and tetanus vaccines) (27).

It was recorded that vaccinated children were exposed more to aluminium (11-26%) than undervaccinated children. "Power analyses demonstrated that safety studies of aluminium could detect relative risks ranging from 1.1 to 5.8 for a range of adverse event incidence" (28). It has been hypothesized that aluminium hydroxide, which was used as adjuvant in multiple vaccines that soldiers underwent, is associated with Gulf War syndrome (29, 30). The Global Advisory Committee on Vaccine Safety of WHO does not find that there is basis at present to change recommendations for vaccination practices (31).

Though, aluminium neurotoxicity is documented, there is common opinion that healthy adults may tolerate repeated oral exposures to aluminium (up to 3500-7200 mg/day from antacids and buffered aspirin) without any toxic effect. It is explained by low absorption and rapid and primarily urinary excretion of Al compounds. But it is clear

that even low daily doses of aluminium can cause systemic intoxication in patients with kidney failure, preterm infants and young children (5).

Effects of aluminium on respiratory system

Aluminium dust has hazardous effect on respiratory system of aluminium production workers. It is shown that they suffer from respiratory symptoms such as cough, wheezing, dyspnea, and chest tightness. Potroom workers who breathe large amounts of aluminium dusts can get wide range of lung diseases: chronic bronchitis, chronic obstructive pulmonary disease, potroom asthma, alveolitis, pneumoconiosis, and even oncological respiratory diseases. All these toxic effects cannot be attributed solely to aluminium. Aluminium potroom workers are exposed not only to alumina dust, but also to particles of fluorides and traces of different elements (vanadium, chromium, nickel), polycyclic aromatic hydrocarbon, mineral dusts (as silica and asbestos), coal tar pitch volatiles, fumes and gases (hydrogen fluoride, carbon oxides, sulfur dioxide, and oxides of nitrogen), extreme heat, and high static magnetic fields (5, 24, 32-34).

Effects of aluminium on bone and hematopoietic tissue

Most of the aluminium that accumulates in body is deposited in the bones (8). Aluminium deposits are found also in the hydroxyapatite of the bone matrix in patients with coeliac disease (due to an increased intestinal permeability) and in the case of long-term use of aluminium anti-acid drugs (35, 36).

Patients with kidney failure due to the toxic effect of aluminium in dialysis fluid developed osteomalacia, osteodystrophy and microcytic anemia and dialysis encephalopathy. Aluminium bone disease is characterized by low serum parathyroid hormone (PTH) levels. Removal of aluminium from the dialysate has resulted in disappearance of the bone disease and in an increase in plasma PTH levels (35). The administration of aluminium in rats with chronic renal failure has resulted in reduction of both synthesis and release of PTH (37).

Although very low doses of Al have mitogenic effect in bones of experimental animals, high doses of Al inhibit remodeling of bone by slowing osteoblast and osteoclast activities (35, 36). In neonatal rat osteoblast tissue culture $AlCl_3$ has been shown to destroy calcium homeostasis, which activates the Ca^{2+}/calmodulin-dependent protein kinase II signaling pathway and thus promotes osteoblast apoptosis (38). Al occupies the unmineralized type I collagen, which is freshly laid down at the mineralization front of the bone surface instead of calcium. The result of impaired bone calcification is development of osteomalacia associated with hypercalcemia, and hypercalciuria (25).

Aluminium chronic intoxication causes a microcytic hypochromic anemia in patients with compromised kidney function (39-41). This anemia is not reversible by iron and it is characterized by decreased red cell count as well as hematocrit and hemoglobin concentration. Pathogenesis factors responsible for Al induced anemia are: shortened erythrocyte lifespan due to reduced erythrocyte membrane integrity; inhibition of δ-aminolevulinic acid dehydratase (42), reduced Fe uptake by transferrin due to competitive interaction between iron and aluminium (43).

Downregulation of transferrin receptor expression and impaired intracellular delivery of Fe from transferrin is also recognized as pathogenesis factor for this type of anemia (39, 40).

Similar values of affinity constant of aluminium and iron for the binding of transferrin receptors are recorded in cultured Human erythroleukemic K562 cells. Opposite to previous findings, it is reported that Al modified Fe uptake without affecting the expression of transferrin receptors. It is concluded that Al induced upregulation of nontransferrin bound iron uptake as an adaptation aimed to enable incorporation of iron which is essential for cellular metabolism (43).

Effects of aluminium on reproductive system

The decline in male fertility, observed in the twentieth century, is a very current issue in contemporary science. Male fertility has declined by 50% over several decades of the industrial revolution. It was not known for a long time about harmful effects of aluminium on male fertility (44-47). Exposure to Al has been reported to affect testicular development and testosterone synthesis in experimental animals (48-51). Although it was shown that Al is capable of compromising male fertility by inducing a state of oxidative stress in the testes (48-52), other mechanisms such as inhibition of microtubule assembly could also be involved in Al-induced testicular damage. Aluminium showed negative impact on reproductive abilities of adult bank voles by causing morphologically abnormal development of the gonads and by decreasing the quality and quantity of sperm (53). Intraperitoneal administration of $AlCl_3$ induced dose dependent decrease of testosterone levels in the testes and plasma of mice (48). In male Swiss albino mice treated intraperitoneally with $AlCl_3$ were observed "deformations of the Sertoli cells, epithelial sloughing, tubular atrophy, and abnormal germ cells" (50). In Wistar rats treated with aluminium sulphate in drinking water is recorded significant decrease of sexual accessory glands: seminal vesicles, prostates, bulbourethral glands and of seminiferous tubules (54). Chronic oral exposure to aluminium at low levels is reported to have as negative impact as high levels on reproductive parameters in Wistar rats. These findings are suggesting adverse impact of aluminium on male fertility (55).

Decreased pregnancy rate was observed in untreated females mated with males treated intraperitoneally with 100 or 200 mg/kg/day of aluminium nitrate for 4 weeks. Treated male mice showed significantly decreased body weight, as well as testicular and epididymal weights. Also, significant decreases in testicular and spermatid counts and epididymal sperm counts were recorded. Sperm moti-

lity and morphology were unaffected. Histological changes manifested as necrosis of spermatocytes/spermatids in the testes, whereas the tubular diameters were unaffected by aluminium administration (56). A negative impact of aluminium on rabbit sperm cell motility and viability has been shown *in vitro* (51). Rabbits orally treated with $AlCl_3$ for 16 weeks had significantly decreased libido, ejaculate volume, sperm concentration, total sperm output, sperm motility (%), total motile sperm per ejaculate, packed sperm volume and total functional sperm fraction. Relative weights of testes and epididymis were also significantly decreased (49). High concentrations of Al in human semen, seminal plasma, spermatozoa, blood, and urine have been linked to poor sperm quality and viability in men (47).

The effects of aluminium on the female reproductive system are not enough elucidated yet. Histopathological changes in the mice ovaries and decreased fertility, after 12 weeks of aluminium chloride administration (dose range 1000-1400 mg/kg) were showed. Both the number of pregnant females and the number of absorbed fetuses were decreased (53). Female mice were exposed by nasal drip during whole pregnancy to Alumina nanoparticles. Aluminium content in hippocampus of newborns was significantly increased. Neurodevelopmental toxicity was registered in the offspring at first month of age as significantly increased anxiety-like behavior with impaired learning and memory performance (57). Subchronic oral exposure to $AlCl_3$ caused the damage of the ovarian structure in rats. Metabolism of Fe, Zn and Cu was disturbed. Activities of Na^+-K^+-ATPase, Mg^{2+}-ATPase and Ca^{2+}-ATPase in ovaries decreased, and expression of follicle stimulating hormone (FSH) and luteinizing hormone (LH) receptors were suppressed (58, 59). The significant decrease of litter size, modification of sex ratio (increase of female pups number), and significant delay of vaginal opening compared to control group were registered in female Wistar rats exposed to aluminium sulphate by drinking water (60). Oral application of $AlCl_3$ (200 mg daily) during 30 days resulted in a significant decline in uterine and ovarian protein levels and in 3β- and 17β-hydroxysteroid dehydrogenase activities. Estradiol levels also declined. Hypercholesterolemia and significant accumulation of cholesterol in the ovaries of treated mice as well as accumulation of glycogen in uterus were reported too. Toxic effect in female mice due administration of aluminium chloride has affected steroidogenesis in ovary, and carbohydrate metabolism in uterus. These effects were reversible upon withdrawal of the treatments (61). In adult female Wistar rats treated with aluminium nitrate, the presence of electron-dense material in lysosomes of myometrium and endometrium cells as well as in the cells of the internal theca and granulosa cells was showed by transmission electron microscopy. Also, impaired endoplasmic reticulum, mitochondria and vacuolation were registered. It was concluded that lysosomes of uterus and ovary cells had defense function and extract aluminium and deposit it in an insoluble form (62).

Effects of aluminium on liver

Aluminium is accumulated in the liver, less than in bones, but the manifestations of Al toxicity in liver have been described. Morphological and morphometric changes highly suggestive of toxic hepatitis were registered in Albino Wistar rats treated with aluminium chloride solved in distilled water intragastrically for 21 days. Architectural derangement was observed as well as degenerative changes at cellular level: nuclear variations such as karyorrhexis and pyknosis (63). In of $AlCl_3$-treated rats a significant rises in plasma levels of AST, ALT, ALP, and LDH in $AlCl_3$ were recorded as well as a significant reduction in total protein level. A significant level of oxidative stress in liver tissue was also registered (64). High doses of Al induce toxic effects and damage the lysosomes in the liver and the extent of lysosomal damage depended of dose and duration of Al loading (65). Accumulation of bile acids in serum in rats and piglets (66), and increased transferrin excretion in the bile were also found (67). Reduction of some cytochrome P450 isoenzymes, nicotine adenine dinucleotide phosphate (NADPH), cytochrome c reductase, and a 4-fold increase in glucuronyltransferase activity were registered in rats treated parenterally with Al. These findings indicate increased conjugating activity (68) and changes in cytochrome P450 isoenzymes may alter metabolism of drugs.

Effects of aluminium on skin

Although absorbed through the skin, aluminium exposure via intact skin is rather mild, confirming this is an effective barrier (69). Aluminium salts, particularly aluminium chlorohydrate, are used in various antiperspirant cosmetics products, as they block secretion of sweat (70).

Following the dermal application of aluminium chlorohydrate penetration rate was very low (around 0.01%) (71). Only insignificant transdermal absorption of Al was shown after application of three different antiperspirant formulations on intact skin. Also, there were low cutaneous quantities of Al ranging 0.5-1.8 μg/cm^2. On the other hand, Al uptake after topical antiperspirant application, through the pre-damaged skin (stripped skin) was significantly higher (0.06% or 11.50 μg/cm^2) (70). In this respect, there was a discussion of whether the breast cancer was associated with the use of Al containing antiperspirants, as a form of aluminium-related chronic diseases (69). However, no significant link between antiperspirants or deodorants use and increased risk for breast cancer was found. A population based case-control study involving 813 breast cancer patients revealed no significant association of regular antiperspirant use or following hair removal 1h after shaving (72).

Intact skin is an effective barrier for Al exposure thus its effects on human keratinocytes are supposed minimal. However, the study of Al nanoparticle interactions with human epidermal keratinocytes showed the particles localization within the cytoplasmic vacuoles of the cells and there was indication of their interactions with cytokine assays

(73). Detrimental effects of Al were shown on human skin fibroblast cultures and were governed by lipid peroxidation as a pathway of Al cytotoxicity. The experiment showed significant malonodialdehyde (MDA) production after 24 h incubation with Al (74). In the perspective, the epidemiological study on internal exposure after antiperspirants use should be performed, and the association with hair removal products or shaving.

Mechanisms of aluminium toxic effects

Clinical and experimental studies suggest several mechanisms of toxic aluminium action on cells. Those are: increased production of oxidative stress, alteration of membrane function, disruption of intracellular signaling, and alteration or inhibition of enzyme functions. All of them may eventually cause tissue damage.

1. Association of aluminium and increased oxidative stress

Large number of studies demonstrated there is a link between increased Al concentrations and oxidative stress. Generally, there are several mechanisms that produce imbalance between free radical production and antioxidant defense system. Aluminium was shown to take part in disruption of metal ion homeostasis and potential oxidative stress through the reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation (75, 76).

Oxidative stress has multiple effects on molecules structure and function, and leads to lipid peroxidation, protein modifications and DNA damage. Aluminium driven oxidative stress was shown to lead to the germ cell apoptosis and decrease in intracellular ATP level (hypoenergosis and motility) (77). Also, its redox state is implicated in a variety of neurological disorders. Another example is Al mediated testicular damage through depletion of antioxidative enzymes protection, and an induction of NO byproducts and consequent inhibition of steroidogenesis (79). Although Al does not undergo redox change, it may enhance iron driven biological oxidation by formation of Al superoxide and by catalyzing H_2O_2 formation while reducing Fe^{3+} (78).

By creating a labile iron pool, a redox-active iron, Al interferes with cellular pathways of iron metabolism. This pool has a capacity to promote ROS generation. It is regulated by cytosolic iron regulatory proteins and dependent expression of iron import and storage machineries, or ferritin degradation or synthesis (80).This relationship was proven in animal model study where Al serum levels were found inversely correlated with Fe serum levels, implying on Al intoxication intervene in Fe metabolism (48).

Al can also displace other biological cations, such as calcium, zinc, copper and magnesium from their binding sites. Thus released ions can catalyze hydrogen peroxide transformation to the highly reactive hydroxyl radical, and further initiate lipid peroxidation (81).

Another mechanism of detrimental Al effect is impairment of mitochondrial bioenergetics, also associated with ROS generation (79). Dysfunction of mitochondrial bioenergetics progressively leads to myocardial failure, because energy insufficiency plays a key role in systolic heart failure (82).

Aluminium was also linked to the production of RNS by induction of NO byproducts. Also, increased ROS, through other mechanisms, reduce the amount of bioactive NO by formation of toxic peroxynitrite. Al administration significantly increased NO production and decreased adenosine 3, 5-cyclic monophosphate (cAMP) and testosterone (83).

Several studies demonstrated that Al may cause changes in antioxidants activity, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase/reductase (84). $AlCl_3$ was suggested to inhibit the activity of superoxide dismutase (SOD). It is demonstrated that one month administration of $AlCl_3$ significantly decreased the activities of SOD, suggesting that Al have catalytic activity for ROS production. Reduced SOD and glutathione peroxidase (GPX) activities might be attributed to the elevated level of protein and lipioxidative products (85).

By decreasing the activity of glutathione synthetase, Al might slow the glutathione (GSH) synthesis, one of the most important antioxidants in cells. It is hypothesized that this process occurs through the depletion of ATP. Particularly, Al forms a strong complex with ATP, as it has high affinity toward phosphate ions, and lowers its availability in the cell (79). Another suggested mechanism of decreased GSH is the insufficient supply of NADPH, due to the Al mediated inhibition of NADPH generation. Al inhibits NADP-isocitrate dehydrogenase, the only enzyme supplying NADPH in mitochondria (86). Al, at doses above 120 mg/kg bw in Wistar rats (orally), produced significant reduction of GSH content and an increase of oxidized/reduced glutathione ratio, in the small intestine mucosa. Also, activities of both GSH synthase and GSSG reductase were significantly reduced. This change in epithelial cells redox state contributed to alteration in GSH-dependent absorptive functions (87).

Al induced oxidative unbalances are associated with lipid peroxidation process. Malondialdehyde (MDA), a lipid peroxidation indicator, is found increased in testis and epididymis after Al exposure (88). Also, lipid peroxidation was found significantly increased in the small intestine when higher Al doses were used (>120 mg/kg) in animal model (89).

2. Aluminium caused alteration of membrane function

The plasma membrane seems to be the target for Al related toxicity, as these trivalent cations readily engaged in interactions with the membrane components thereby affecting associated processes. Al may form electrostatic bonds with oxygen donor ligands or interact with the membrane lipids (79). Also, it may directly alter electrical potential and membrane surface potential (89). Interestingly, binding of Al to the membrane lipids causes the membrane to become more rigid, which ultimately affects the cell motility and viability (90). Production of ROS and lipid peroxidation of membrane lipids has profound and progressive negative consequences. It hinders membrane fluidity (to become rigid), increase permeability, alter r

eceptor function, etcetera (79). All these changes further influence intracellular processes such as enzyme inactivation, DNA damage and cell death. Chronic aluminium-in-duced neurotoxicity has been related to lipid per-oxidation of the brain cells that probably arises from altered lipoprotein metabolism (91).

3. The channel hypothesis of Alzheimer's disease (AD)

There are controversies about ion channel hypothesis for Alzheimer amyloid peptide neurotoxicity. According to some reports beta-amyloid (Aβ) peptides which accumulate in plaques in the brain in Alzheimer's disease can form ion channels in lipid bilayers. liposomes, neurons, oocyctes, and endothelial cells. These channels are heterogeneous in size, voltage-independent, and poorly selective for ions and they can allow influx of (Ca^{2+}), Na^+, K^+, Cs^+, Li^+, and possibly Cl^- (18). Overload with positive ions may damage and/or kill neurons.

There is no doubt that Aβ is capable to induce transmembrane ion fluctuations in living cells. But in more recent report are presented data which suggest "that Aβ is capable of self-assembling into structures that either form a pore through membranes or generate transient defects in membranes". It is concluded that Ca^{2+} influx through Aβ-induced pores or membrane defects and disruption of Ca^{2+} homeostasis could contribute to development of Alzheimer's disease. These authors left open the possibility that Aβ activates intrinsic ion channels or ion pumps in cells (92).

4. Aluminium and disruption of intracellular signaling

Several intracellular signaling pathways are reported to be modified by Al ions. Al was found to disturb secondary messenger signaling, including cAMP, Ca^{2+}, and phosphoinositide and inositol-1, 4, 5-triphosphate (IP_3), all of which are involved in a variety of processes, ranging from cell growth, differentiation to apoptosis (93).

Aluminium alters cyclic AMP and cyclic GMP levels (less sensitive than AMP). Al has elevated cyclic AMP levels in rat cortex following oral administration for 4 weeks. Supposed mechanism is a G-protein stimulation of adenylate cyclase as Al may replace the Mg^{2+} that confers the structure to the triphosphate of GMP (94).

Al is reported as an effective voltage sensitive calcium channel blocker. It blocks Ca entry into the cell and inhibits Ca^{2+}/Mg^{2+}-ATPase (on endoplasmic reticulum) dependent sequestration of Ca^{2+} from the cytosol. Al action in this process is complex as it increases the activity of the Ca^{2+} ATPase, similarly to Mg^{2+}, but also displaces these two molecules and thus disrupts calcium transport (95). When applied extracellularly, Al reduces voltage-activated calcium channel currents in a concentration and pH dependent manner and irreversibly (96).

Al interference with IP_3 and its intracellular depletion is based on Al^{3+} much higher affinity for the phosphatidylcholine surface than Ca^{2+} (additionally disturbing Ca homeostasis) (97).

5. Aluminium caused alteration of enzyme functions Nikotinamide Adenine Dinucleotide Phosphate

Taking into account previously described mechanisms of Al action it can be concluded that there is substantial influence on cellular protein function and metabolism. Its effects on proteins are varied, ranging from alteration in their expression due to the Al binding to deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), to direct inhibition of several enzymes such as hexokinase, phosphatases, phosphodiesterase and phosphooxydase, glucose-6-phosphate dehydrogenase and NADP isocitrate dehydrogenase. For example, Al inhibits hexokinase because it changes Mg ion in Mg-ATPase, a hexokinase substrate (97). Or, by perturbation of intracellular Fe metabolism and Fe-S cluster Al promotes the inhibition of aconitase activity, enzyme involved in metabolism of citrate, in Pseudomonas fluorescens (98).

Al exposure ($AlCl_3$) induced significant change of intestinal enzymes, as well as expression of the multidrug resistance-associated protein 2 which was nearly 3-fold increased. Gamma-glutamyltranspeptidase activity was also increased, while glutathione (GSH) synthase and glutathione disulfide (GSSG)-reductase were decreased (87).

By changing phosphoinositides metabolism Al causes cytoskeletal rearrangements and abnormalities, which alter cellular motility and viability (78). Already mentioned increased NO production by Al may react with superoxide or hydrogen peroxide to generate more reactive compounds which cause oxidation of thiol proteins (79).

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PATOFIZIOLOŠKI MEHANIZMI ALUMINIJUMSKE TOKSIČNOSTI

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Aluminijum čini oko 8% minerala zemljine kore. Najčešće se nalazi u obliku boksita rude koja se koristi za dobijanje tog metala. Aluminijum je visoko reaktivan i formira jedinjenja kao što su aluminijum-oksid, aluminijum-hidroksid i natrijum-aluminijum-sulfat. U kontaktu sa oksidansima, ta jedinjenja stvaraju površni pasivizirajući sloj aluminijum-oksida, koji sprečava koroziju i čini ga nerastvorljivim u vodi. Međutim, kisele kiše omogućavaju rastvaranje tih jedinjenja i ulazak aluminijuma u biološke sisteme. Aluminijum može ući u ljudski organizam preko vode, hrane, lekova i udisanjem zagađenog vazduha. Nakon što se akumulira u telu, on ispoljava toksične efekte na: centralni nervni, respiratorni, hematopoetski, reproduktivni, digestivni (jetru) i koštani sistem. Toksični sistemski efekti aluminijuma najpre su uočeni kod bolesnika sa bubrežnom insuficijencijom, lečenih lekovima koji sadrže aluminijumska jedinjenja (dijalizna encefalopatija, osteomalacija sa osteodistrofijom i mikrocitna anemija).

Aluminijum je u vrhu kratke liste neurotoksičkih neorganskih elemenata i njihovih jedinjenja. Povezuje se sa razvojem neurodegenerativnih bolesti, uključujući autizam, poremećaje pažnje, amiotrofičnu lateralnu sklerozu, Alchajmerovu bolest, demenciju, sindrom Zalivskog rata i parkinsonizam. Kliničke i eksperimentalne studije ukazale su na više mogućih mehanizama kojima aluminijum toksično utiče na ćelije. Tu spadaju: povećana produkcija oksidativnog stresa, promena funkcije membrana, poremećaj intracelularne signalizacije i promena ili inhibicija funkcije enzima.

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Ključne reči: *aluminijum, toksičnost, oksidativni stres, neurodegenerativne bolesti, patogeneza*