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When chemistry meets biology: the case of aluminium – a review

Vilma Kisnierienė,

Indrė Lapeikaitė

Department of Neurobiology and Biophysics,
Faculty of Natural Sciences,
Vilnius University,
M. K. Čiurlionio St. 21/27,
LT-03101 Vilnius, Lithuania

Aluminium chemistry is extraordinary and complex because of a large spectrum of inorganic and organometallic complexes of varying stability in solutions. Being reactive, aluminium has the potential to interact with and influence many biomolecules, biochemical pathways, cellular processes and physiological functions, thus causing high Al toxicity. It depends not only on the total Al concentration but also on the abundance of Al chemical forms, Al speciation being highly dependent on the pH and chemical environment of the solution. The oxidative potential of aluminium leads to enhanced oxidative stress, which explains part of Al toxicity mechanisms. Al is a known pro-oxidative, cytotoxic, neurotoxic, immunogenic, pro-inflammatory and mutagenic agent. Usually, organisms are not exposed to relevant levels of aluminium but long-term accumulation causes several human diseases and disturbs plant growth. In contrast to animals and humans, plants evolved specific mechanisms to cope with Al stress. We review the existing knowledge about aluminium chemical properties, bioavailability and cell responses determining Al toxicity not only in humans but also in plants. Extraordinary chemistry of Al and complexity of biological processes require complex researches to link knowledge of Al chemistry and biology of its effects in order to find the best solution to resist the aluminium toxicity.

Key words: aluminium, aluminium bioavailability, aluminium toxicity, aluminium related diseases, plant resistance to aluminium

INTRODUCTION

Aluminium is the third most abundant element in the earth's crust after oxygen and silicon, and the most abundant metal. Its atomic number is 13 and it has one stable isotope, ^{27}Al, and one long-lived radioactive isotope, ^{26}Al. Bound tightly by oxygen and silicon, Al exists naturally in ores generically termed bauxite. Bauxite consists mainly of the hydrated aluminium oxide ($Al_2O_3 \times H_2O$) minerals, gibbsite, boehmite, and diaspore. Despite its abundance, Al was first isolated as an element only in 1827, and its use as being a silvery metal began only after 1886. The electrolytic process, still employed nowadays, was separately patented in France and the USA in 1886 [1].

The protective layer of oxide in addition to its light weight makes aluminium metal an ideal material for many applications in the industry. The 'aluminium environment' acted upon by natural selection is changing, and through human activities, not least of which has been the technology to extract aluminium metal from its biologically inert ores, biota are experiencing a burgeoning exposure to biologically reactive aluminium [2].

An increase in anthropogenic acidification of soils, the increased utilization of the metal for industrial purposes, and Al utilization as a flocculent in water treatment and hiding him in food additives or cosmetics make aluminium harmful not only for humans but for all life forms in the earth.

Generally Al is not essential for life but because of extremely high reactivity in its pure elemental form Al has a tremendous impact on life [2]. Aluminium interferes with a wide range of physiological and cellular processes. As Al is highly reactive, there are many potential sites for injury in all living systems. Aluminium is a widely recognized toxicant that inhibits more than 200 biologically important functions and causes various adverse effects in plants, animals, and humans [3]. The mechanism of toxicity of aluminium is invariably biphasic with lower concentrations producing toxic effects through stimulatory

* Corresponding author. E-mail: vilma.kisnieriene@gf.vu.lt

actions and higher concentrations resulting in inhibition of essential processes and pathways [4]. Al can cause severe health problems in particular populations, including infants, elderly people, and patients with impaired renal functions. Al has been cited as the cause of encephalopathy, dementia and impaired neurological development, osteopenia, and osteomalacia [5]. Root growth inhibition is a major consequence of Al toxicity in plants [6].

In contrast to animals and humans, some species of plants grow in acidic environment where Al is toxic. As a part of natural selection, plants evolved some specific mechanisms to cope with Al toxicity. The toxicity of Al to plants, aquatic life and humans may share common mechanisms, related to not ordinary chemistry of this metal. Knowledge get from plants might explain Al action and toxicity mechanisms in every cell and propose solutions in human disease treatment.

We review here knowledge about aluminium chemical properties, bioavailability and cell responses which determine Al toxicity not only in humans but also in plants.

Chemical properties of Al

Aluminium chemistry is extremely complex and still not fully understood because of a large spectrum of polynuclear inorganic and organometallic complexes of strongly varying stability that occur in natural soils and waters. Aluminium toxicity depends not only on the total Al concentration but also on the Al chemical forms, with Al speciation being highly dependent on the pH and chemical environment of the solution. Except in biological and/or environmentally acidic situations, aluminium remains tightly bound to oxygen in geological stores. Al(III) ions occur as silicates or hydroxide complexes under neutral pH conditions in which there is no appreciable toxicity by Al(III) because of the extremely low solubility of the ion. Any free native Al(III) is immobilized in the soil as an insoluble hydroxide. The chemistry of aluminium in geological stores is very strongly related to the capacity of aluminium to form an Al–O 'passivation layer', however, this reactivity situation changes when aluminium is exposed to the complex mixtures of oxygen donor ligands. Acidifying substances such as NO_x, NH_3 or SO_x are emitted to the environment by industry, traffic, agriculture and households. NO_x, and SO_x are transforming in the atmosphere to strong acids, which move in short to long distances and settle onto the soil as wet or dry depositions. NH_3 transforms in the air to NH_4^+ which in soil may be nitrified ($NH_4^+ + 2O_2 \rightarrow 2H^+ + NO_3^- + H_2O$), releasing protons into the soil solution. Acid deposition might accelerate soil acidification below approximately 5.5 pH. In this range, acidity starts to dissolve pedogenic aluminium compounds and the proton buffering is followed by a release of free aluminium cations into the soil solution. Al easily transits from the solid to liquid phase at low pH values, where Al(III) ions are mobilized and exert toxic effects on many living organisms.

When the metal is no longer bound by its mineral deposits, it flows into fresh water. Consequently soil acidification may lead to severe stream and lake acidification thus aluminium concentrations became noticeable in rivers and lakes where the pH is lower than 6. Elevated Al^{3+} stock, that has been shown to adversely impact lower food-chain, is subsequently transferred (i. e. phytoplankton–zooplankton) to the higher components of the food chain.

Estimation of Al^{3+}activity and of different inorganic and organic Al species in complex solutions can be achieved by speciation programs (e. g. ALCHEMI, GEOCHEM, MINEQL+) [7].

The hydrolysis of aluminium greatly affects its solubility and the bioavailability in biological environments. Al(III) is often found as polymeric species, in which OH^- usually coordinates two or more $A1^{3+}$ ions. The number of water molecules in this first sphere of coordination is six, and these water molecules are regularly coordinated in an octahedral geometry, forming the species $[Al(H_2O)_6]^{3+}$, usually abbreviated as Al^{3+}. At pH < 5 the main species is the hexaaqua ion $[Al(H_2O)_6]^{3+}$ or Al^{3+}; as the pH increases, the new mononuclear species, $Al(OH)^{2+}$, $Al(OH)_2^+$, and the soluble neutral species $Al(OH)_3$ are formed by deprotonation of coordinated water. Polinuclear species are also formed, the principal ones being $Al_2(OH)_2^{4+}Al_3(OH)_4^{5+}$, whose relative concentrations depend on the total aluminium concentration [8]. For example, at relatively high concentrations of Al^{3+} (≥100 μg/L) in the pH range 5.3 to 6.5, polymerization occurs and results in the formation of polynuclear species such as $Al_{13}O_4(OH)_{24}^{7+}$ [9]. At neutral pH the solid $Al(OH)_3$ precipitates and at higher pH it transforms in the soluble $Al(OH)_4^-$. At pH 7 the total soluble concentration decreases to 7 μg/dm^3 because of $Al(OH)_3$ and in a negligible quantity to $Al(OH)_2^+$ and $Al(OH)_4^-$. Thus at physiological pH of 7.4, little or no free (hydrated) Al^{3+} exists in an aqueous solution and the anion $Al(OH)_4^-$ predominates. At pH 8 the contribution of $Al(OH)_4$ is highest [10]. The speciation of the soluble and insoluble forms of hydroxo complexes is of primary importance to describe the solution chemistry of aluminium in biological systems. The mononuclear Al^{3+} species are considered the most toxic form.

Interaction of Al with biologically important compounds

Aluminium(III), with an ionic radius of 0.54 Å, is the "hardest" of the trivalent metal ions, with effective ionic radius smaller than that of iron(III) and gallium(III). Al^{3+} has strong positive charges and a relatively small ionic radius in comparison to other metal ions such as Ca^{2+}, Zn^{2+}, and Na^+. Al^{3+} has a very low ligand-exchange rate in comparison to other metals [8]. Due to the strong selectivity of the cation exchanger for trivalent cations, aluminium gradually replaces the divalent and monovalent nutrient cations (Ca^{2+}, Mg^{2+} and K^+) from their exchange sites. The Al entry into the cytoplasm affects the homeostasis of various ions, such as H^+ and K^+, [11] Ca^{2+} [12]. Both Al^{3+} and Mg^{2+} ions are hexahydrates, with the hydrated radius of Al^{3+} (0.480 nm) and Mg^{2+} (0.428 nm) being remarkably similar; hence, the Mg^{2+} uptake system or

the Mg^{2+}-binding sites on enzymes do not distinguish well between Al^{3+} and Mg^{2+} ions. The Al^{3+} and Mg^{2+} ions compete for membrane transporters [13] and metal-binding sites on enzymes [14]. For example, the ligand-exchange rate of Mg^{2+} is 10^5 times faster than that of Al^{3+}, and therefore, Al^{3+} inhibits enzymes with Mg^{2+} cofactors [8]. ATP might be the most important binder of Al(III) in cells, and Al^{3+}competes with Mg^{2+} for binding to ATP [15]. Al^{3+} also inhibits biological processes involving rapid Ca^{2+} exchange: the exchange rate for Al^{3+} is 10^8 times slower than that of Ca^{2+}. It has been suggested that the displacement of Ca from the membrane surface by Al may increase the apoplastic Ca pool in plants [12]. In humans approximately 70% of the aluminium body burden is localised in the skeletal system [16]. A release of phosphorus (P) from roots or from chemical compounds in the rhizosphere has the potential to be an Al resistance mechanism in plants because phosphate ions strongly bind to Al^{3+} to form non-toxic Al–phosphate complexes either in the apoplasm, on the root surface, or in the rhizosphere [17].

Al exhibits only one oxidation state Al^{3+} and has affinity for negatively charged, oxygen-donor ligands. So there are many biologically important compounds which can bind Al^{3+}. In biological systems, oxygen donor ligands typically include carboxylates, organic and inorganic phosphates, nucleotides, and polynucleotides such as DNA and RNA in all of their structural forms. Deprotonated hydroxyl groups form strong bonds with Al^{3+}, also Al^{3+} binds to the phosphate groups of nucleoside di- and triphosphates, such as ATP and can thus influence energy metabolism. It was shown that an astrocyte cell line exposed to varying concentrations of Al experienced a sharp decrease in ATP synthesis [18]. Furthermore, Al tends to slow reactions, especially of phosphates, in all organisms, so Al inhibits the functions of various protein kinases and phosphatases [8]. It has been shown that Al can act upon the signal transduction pathway specifically reducing the activity of phospholipase C, consequently followed by inhibition of IP_3, regulation of calcium release and activation of protein kinases [19].

Al^{3+} firmly binds to metal-binding amino acids, histidine (His), tyrosine (Tyr), arginine (Arg), etc. or phosphorylated amino acids and acts as a cross-linker. By binding to various proteins, Al can cause the oligomerization of proteins, inducing conformational changes that can inhibit their degradation by proteases. Strong binding of Al^{3+} to phosphorylated amino acids promotes the self-aggregation and accumulation of highly phosphorylated cytoskeleton proteins, including neurofilaments and microtubule-associated proteins [15]. Aluminium citrate promotes aluminium deposition in the parotid and submandibular glands, leading to an increased expression of MT-I/II, damages the cytoskeleton of the myoepithelial cells in both glands [20].

Aluminium could bind to membrane lipids, particularly with those negatively charged phospholipids (phosphatidylserine), causing changes in membrane physical properties [21].

The activity of (Na^+/K^+)ATPase is altered by the microviscosity of lipid environment, so the aluminium effect on (Na^+/K^+)ATPase activity seems to implicate the reduction of interacting protomers within the oligomeric ensemble of the membrane bound (Na^+/K^+)ATPase [6, 22].

Aluminium efficiently aggregates several different classes of organic molecules in solution, such as amyloid peptides, non-amyloid components, cell cyto-structural neurofilaments, phosphoproteins, glycoproteins and small, irregularly-shaped anuclear cells also known as thromobocytes (blood platelets) [15]. Further, aluminium has also been shown to associate with aggregated amyloid plaque cores, which may be in a relatively non-specific fashion, but have immunopathological and pro-inflammatory consequences in neurodegenerative brain disease [23].

The distribution of aluminium in the blood serum is well established: Al is bound to transferrin with a high affinity, approaching its affinity for iron and transferred to receptors. Transferrins (Tfs) are a group of iron (Fe)-binding glycoproteins and the most important iron transporter. Albumin, the other serum protein, was found to be not efficient enough in binding Al(III) in the presence of Tf [10].

Being so reactive, aluminium interacts with and influences many biomolecules, biochemical pathways affecting cellular processes and physiological functions.

The effect of Al on DNR

Data report a relatively strong binding of Al(III) to DNA and RNA, which occurs with the phosphate backbone under neutral pH conditions [24]. Al^{3+} binding affects DNA topology and influences the expression of various genes essential for life functions. How Al induces DNA damage is not known, although a likely mechanism is the induction of oxidative damage [25]. It was demonstrated that Al promotes the generation of iron-induced reactive oxygen species (ROS) [26]. There is evidence that Al induces chromosomal aberrations, micronuclei and sister-chromatid exchanges in human lymphocytes [27]. Furthermore, Al can accumulate in the nuclei of plant cells in the meristematic region of the root tip within 30 minutes [28]. Lukiw et al. reported that nanomolar levels of Al^{3+} were sufficient to influence neuronal gene expression [29].

The analysis of the comet assay results showed that Al induced human lymphocytes DNA damage in a dose-dependent manner, reaching its maximum after a dose of 10 μg/ml. Treatment of cells with 25 μg/ml of Al resulted in a decreased level of DNA damage and a concomitantly increased frequency of apoptotic cells [27].

Al impact on calcium homeostasis and skeleton

Al^{3+} disturbs calcium metabolism by interfering with Ca^{2+} signalling pathways, blocking Ca^{2+} channels and competing with Ca^{2+} for other ligands. Al^{3+} competes directly with Ca^{2+} for Ca^{2+} sites on membrane surfaces, on molecules in the cytoplasmic matrix and in membrane Ca^{2+} channels. Al competes with both Ca^{2+} and Mg^{2+} for small ligand oxygen donors such as carboxyl and carbonyl groups, phosphate groups, inorganic phosphate, nucleotides and polynucleotides [30]. Healthy cells

have mechanisms that control intracellular Ca^{2+} content. This requires normally functioning Ca^{2+} transport mechanisms, Ca^{2+} buffering proteins and intracellular Ca^{2+} storage systems. Ca^{2+} levels were found twice as high in brains of Al-treated animals as in brains of unexposed controls [31]. Astrocytes cultured in the presence of 100, 200, or 400 μM Al^{3+} for 1 day show a significant (>50%) dose-dependent increase in their basal Ca^{2+} level compared with that of unexposed controls. Their basal Ca^{2+} level further increases in a time-dependent manner by 130% when Al^{3+} exposure is lengthened to 6 days [32]. Al can effect elevation of the resting Ca^{2+} and peak Ca^{2+} levels in cytoplasm, causing less Ca^{2+} influx and a modest inhibition of phosphoinositide 4,5-biphosphate (PIP2) hydrolysis by phosphoinositide-specific phospholipase C (PI-PLC) in phosphoinositide signaling pathways, resulting in less inositol triphosphate (IP_3) availability for signalling and protein kinase C (PKC) activation; also Al leads to a slower rate of Ca^{2+} removal from the cytoplasm [33]. Al^{3+} interferes with Ca^{2+} signalling by restricting both inositol triphosphate- and caffeine-evoked Ca^{2+} release from endoplasmic reticulum stores. In plants, Al toxicity displaces Ca^{2+} from the plasma membrane, disrupts the signalling cascades of cytosolic Ca^{2+} and blocks ion-channel pumps [12]. Cytoplasmic Ca^{2+} disturbance of cytoplasmic Ca^{2+} homeostasis is believed to be the primary target of Al toxicity and may be involved in the inhibition of the cell division or root elongation by causing potential disruptions of Ca^{2+}-dependent biochemical and physiological processes [6].

When aluminium accumulates in bones, the process of bone formation is disrupted, and osteodistrophy, subsequently better defined as "aluminium-induced bone disease", develops, ending with spontaneous fractures [34]. Aluminium exposures during neonatal and pediatric parenteral nutrition can impair bone mineralization and delay neurological development [35].

Aluminium and cytoskeleton interaction

Aluminium's similarity to iron, in terms of ionic size, allows aluminium to use iron-evolved mechanisms to enter the highly active, iron-dependent cells responsible for memory processing. Aluminium particularly accumulates in these iron-dependent cells to toxic levels, dysregulating iron homeostasis and causing microtubule depletion [36]. Microtubules and microfilaments are altered in their stability, organization, and polymerization, when exposed to Al [37]. The toxicological effect of the Al on the cytoskeleton was not triggered by the reduction in the expression of actin, but was rather caused by the inability of the actin to form a filamentous cytoskeleton. Actin levels were similar in both control and Al-stressed human astrocytoma cells [38].

Aluminium depolymerizes cortical microtubules in living root cells of intact *Arabidopsis* seedlings [39]. The maintenance of cytoskeletal configuration is inherently dependent on ATP because the polymerization of actin relies on a steady supply of ATP. Al-induced disruption of energy in astrocyte results in the inability of the actin cytoskeleton to polymerize, thus causing the loss of cellular morphology [18].

Al and oxidative stress

Al^{3+} itself is not a transition metal and therefore cannot catalyse redox reactions or elicit an increase in oxidative damage, however, it has a powerful pro-oxidant effects both in vivo and in vitro, and exposure to Al leads to enhanced oxidative stress [40]. Al can increase the Fe-induced production of ROS, plasma membrane lipids peroxidation in combination with iron [41, 42]. A number of hypotheses have been proposed for Al^{3+}-induced rapid production of ROS, including dysfunction of mitochondria, formation of aluminium superoxide semi-reduced radicals [43], and activation of oxidizing enzymes [44].

Aluminium catalyses both iron and non-iron mediated biological oxidation. A mechanism has been elucidated to explain the oxidative potential of aluminium and it implicates the binding of Al^{3+}(aq) by the superoxide radical anion ($O_2^{-\bullet}$) to form an aluminium superoxide semi-reduced radical ion:

$$O_2^{-\bullet} + Al^{3+} \leftrightarrow AlO_2^{2+\bullet}.$$

The formation of $AlO_2^{2+\bullet}$ has significant implications for biological oxidation as it both catalyses the (1) formation of H_2O_2 and (2) reduces Fe(III) to Fe(II) [45]:

$$2O_2^{-\bullet} + 2Al^{3+} \leftrightarrow 2AlO_2^{2+\bullet}(2H^+) \rightarrow H_2O_2 + O_2 + 2Al^{3+}, \quad (1)$$

$$Fe^{3+} + AlO_2^{2+\bullet} \rightarrow Fe^{2+} + O_2 + Al^{3+}. \quad (2)$$

Al-superoxide anion complex ($AlO_2^{2+\bullet}$), which is a more potent oxidant than superoxide anion ($O_2^{-\bullet}$) on its own promotes the formation of hydrogen peroxide (H_2O_2) and hydroxyl radicals ($^{\bullet}OH$) through the Fenton reaction by reducing Fe(III) to Fe(II), further contributing to an oxidizing environment [26] and altering the activities of antioxidant enzymes in cells [40] such as superoxide dismutase, catalase and glutathione peroxidase as showed in lymphocytes of the common carp *Cyprinus carpio*, in this case the degree of damage induced was concentration and exposure time dependent [46].

Thus synergism between Al^{3+} and Fe^{2+} results in significantly elevated peroxide levels in cells, peroxidative damage, and oxidative stress [47] which may harm several components of the cell, though in plants there is dependence regarding the plant species [48].

Al causes oxidative damage by binding to pro-oxidant metals besides iron, e. g. copper, modulating their ability to promote metal-based oxidative events because aluminium ions form electrostatic bonds preferentially with oxygen donor ligands (e. g. carboxylate or phosphate groups), and especially targeting cell wall pectin and the outer surface of the plasma membrane. These structures seem to be major targets of aluminium [49].

Al binding to biomembranes leads to rigidification which seems to facilitate the radical chain reactions by iron ions and enhance the peroxidation of lipids [6]. The Al accumulation causes changes in the membrane structure and function, affecting aggregation, fusion and changes in the permeability of liposomes and packaging of fatty acids of the plasma membranes, also membrane proteins can increase the membranes rigidity, likewise by the radical chain reactions mediated by Fe ions enhancing the production of reactive oxygen species [45, 50].

The toxic effects of Al mediated by free-radical generation and toxic consequences also result in mitochondrial dysfunction and may ensure oxidative damage leading to the oxidation of mitochondrial DNA, proteins and lipids[42].

Regarding mammals, in vivo and in vitro assays have suggested that Al affects human erythrocytes through disrupting iron metabolism affecting enzymes required for heme biosynthesis and catabolism and/or cell membrane binding that leads to morphological changes of red blood cells. Long-term or short-term exposure to Al significantly induces HO activity in the liver of rats and mice. Increased HO activity results in the destruction of heme and/or heme proteins, and is hypothesized as a mechanism for Al-induced anemia [51].

Al-overload in rat liver leads to transcriptional and translational activation of the stress responsive gene, *HO-1*, which is correlated with increase H in O activity [52].

Plants encountering aluminium

In plants a major consequence and one of the earliest responses to Al-toxicity is the inhibition of root growth. Root elongation tests have shown that $AlO_4Al_{12}(OH)_{24}(H_2O)_{12}^{7+}$ is the most phytotoxic Al species [49]. There is consensus that trivalent cationic Al^{3+} present as $Al(H_2O)_6^{3+}$ in acid environments is the most relevant toxic form to plants [53]. Cell walls and intercellular spaces, the so-called apoplast, are the first compartments of the root that contact with the potentially toxic Al species present in the soil solution. The cell membrane also provides potential binding sites for Al such as carboxyl and phosphate groups. Binding of Al to the plasmalemma can account for changes of the key properties of this membrane such as fluidity and lateral lipid phase separation leading to changes in the membrane potential [54] and ion channel activity, to alteration of Ca homeostasis [12], to inhibition of proton adenosine triphosphatase (H^+-ATPase) [55], and to lipid peroxidation [56]. In our laboratory we investigate the effect of Al on electrical properties of plant cells as changes in the plasma membrane potential or modulation of ion flux which are amongst the earliest plant cellular events in response to environmental stimulation. Al^{3+} has the potential to affect membrane bioelectricity by directly interacting with the membrane or by affecting channels and H^+-pump. The effect of aluminium on the membrane potential and the generation of action potential were examined by comparing membrane potential dynamics and the shape of the action potential before and after treatment with Al in various pH solutions. We found that the effect of aluminium on the membrane potential depends on pH. We observed a statistically significant depolarization of the membrane potential from −219 ± 12 mV to −160 ± 8 mV after the 1 mM aluminium treatment at pH 4.2. The amplitude of the action potential depended on pH *per se*, but Al^{3+} attenuated its value by 66 mV. Amplitude decrement depends on membrane potential depolarization, whereas the AP peak after the Al^{3+} treatment slightly increased (Fig. 1). Our investigations have shown that Al^{3+} affects electrical characteristics of internodal *Nitellopsis obtusa* cells.

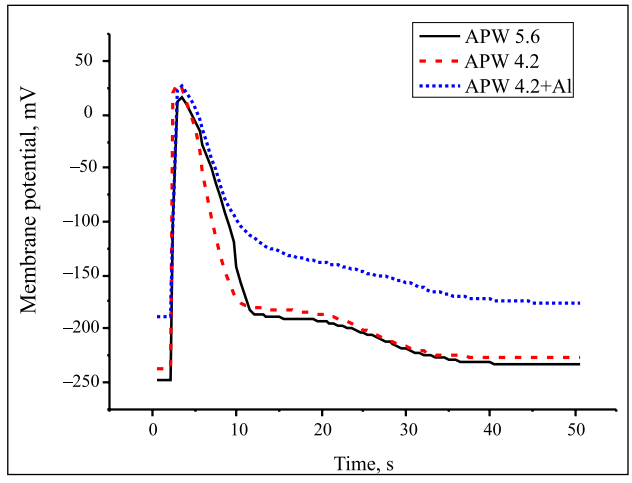

Fig. 1. A typical example of the cell action potential after the 1 mM aluminium treatment in APW (containing 0.1 mM KCl, 1.0 mM NaCl, 0.1 mM $CaCl_2$, 2.5 mM TRIS, adjusted required pH by HEPES). pH 5.6, APW pH 4.2 and APW pH 4.2 + Al^{3+} solution. Amplitude decrement in Al^{3+} solution depends on membrane potential depolarization (blue line).

In higher plants Al can strongly interact with the negatively charged plasma-membrane surface, and thus, for example, affects the activity of the mitochondrial respiration chain. After entering into the cytosol ionic Al rapidly disrupts root cell expansion and elongation by targeting multiple cellular sites and subsequently quickly inhibits the uptake of water and nutrients resulting in poor growth [7]. Al^{3+} toxicity may also (like in any cell) provoke mitochondrial dysfunction [57] and ROS production in many plant species, presumably by causing Mg^{2+} deficiency inside the mitochondria or substituting Mg^{2+} for Al^{3+} in Mg^{2+}-dependent enzymes [13]. It was shown that aluminium reduces ionizing radiation resistance in plants [58].

The cellular target of oxidative stress depends on plant species [6]. At low Al concentrations, the leaf antioxidant defence system can scavenge reactive oxygen species and sufficiently protect cells from free radical injury. However, in higher Al concentrations (e. g. 0.53 mM in tea plant *Camellia sinensis* (L.)) the balance between the formation and detoxification of ROS is lost, indicating Al induces lipid peroxidation and ROS accumulation in tea leaves, therefore resulting in the

destruction of cell ultrastructure [59]. A relationship between aluminium toxicity, endocytosis, endosomes and vesicle recycling in the root transition zone has been demonstrated, thus plant cytoskeleton could be a cellular target of Al phytotoxicity [60, 61]. All these effects have often been described as features of the Al toxicity syndrome [62]. Therefore, root growth inhibition has been widely used to assess Al toxicity. Al toxicity has therefore been recognized as a major factor limiting crop production on acid soils.

However, considering that Al is the most abundant metal in the earth's crust and plants always have the possibility to be exposed to Al stress for a long time of evolution, it is not surprising that plants have evolved specific mechanisms for the Al detoxification via apoplastic or symplastic ways. Two mechanisms, namely, the exclusion mechanism and tolerance mechanism, have been proposed to govern Al^{3+} resistance in plants. Both mechanisms are related to mitochondrial activity as well as to mitochondrial metabolism and organic acid transport [63]. Apoplastic mechanisms include cell wall binding of Al (preventing transfer of Al into the symplast), root secretions that raise proximal soil pH (making Al less bioavailable), and exudation of organic acids or mucilage that complex Al (reducing Al mobility) [64].

The internal Al detoxification mechanism involves chelation of cytosolic Al by organic acid anions and subsequent sequestration into the vacuole. Compartmentalization in vacuoles, where Al does not interfere with the metabolic activities of the cell, is another mechanism type for the Al detoxification [62].

Some plant species tolerate Al in the symplast, often by storing it in less toxic forms, complexed with organic acids. As the oxalate in the cytosol is constitutively high and increasing with Al accumulation, Al is present in the cytosol as $Al(Ox_2)^-$ and may be stored in the vacuoles even as $Al(Ox_3)^{3-}$. In the cytosol $Al(Ox_2)^-$ is transported through the endodermis into the central cylinder where a ligand exchange to citrate, leading to a rather stable $Al(Cit)^{n-}$ anionic complex, is taking place in the xylem parenchyma cells [65].

Depending on the plant species, Al activates exudation of various organic acid anions, such as malate, citrate, oxalate, pyruvate, and/or succinate [53], through organic-anion-permeable plasma membrane channels [66]. Organic acids can bind Al(III) ions tightly, it is expected that they act as Al detoxification reagents inside and/or outside of the cell. The overexpression of enzymes involved in organic acid metabolism caused increases in organic acid secretion and enhanced Al(III) tolerance in transgenic plants [67]. The malate transporter gene isolated from wheat enhanced the Al(III) tolerance of engineered barley plants [66]. The ALMT1 gene (Al-activated malate transporter) in *Triticum aestivum* root cells, which codes for a plasma membrane anion channel that allows efflux of organic acid anions, such as malate, citrate or oxalate, was identified [68]. AtMATE, a homolog of the discovered sorghum and barley Al-tolerance genes, was shown to encode an Al-activated citrate transporter in *Arabidopsis* [69]. Han et al. isolated the Al-induced gene (mitochondrial citrate synthase 1) from *O. sativa* (OsCS1). Several transgenic lines of *N. tabacum* in which OsCS1 was overexpressed exhibited increased citrate efflux and higher tolerance to Al [70].

Al accumulates in the form of Al–citrate (1:1), Al–oxalate (1:3) and Al–oxalate (1:1, 1:2 and 1:3) complexes, respectively [62]. It was shown that Al might be translocated as a complex with citrate in the xylem sap of this plant while Al–oxalate is a major Al complex in roots of tea plant [71]. Al tolerance is not directly linked with an increased expression of genes encoding enzymes responsible for organic acid biosynthesis but rather with a differential expression of transporters [63].

Tolerance of plants to Al-toxicity is associated not only with low Al uptake but also with relatively little Al translocation from roots to shoots [72]. Efficient immobilization of Al by phosphorus in roots might contribute to the Al-tolerance of plants. It was shown that phosphorus can alleviate Al-toxicity through increasing the immobilization of Al in roots and the P level in seedlings rather than through increasing organic acid anion secretion [73].

The alleviation of Al-toxicity by Boron was also shown. Boron appears to alleviate Al-toxicity in *Citrus grandis* roots by the following several aspects: improving the total ability to scavenge ROS and aldehydes; increasing the expression levels of genes related to lipid (i. e. carboxylesterases and lecithin-cholesterol acyltransferase-like 4), amino acid (i. e. nicotianamine aminotransferase A-like isoform X3), sulphur (i. e. thiosulfate sulfurtransferase 18-like isoform X1) and energy (i. e. root isozyme ferredoxin (Fd)-NADP reductase) metabolisms; and upregulating gene expression related to cell transport (i. e. non-specific lipid-transfer protein-like protein At2g13820-like and MFS protein) [74].

It was proposed that plants with more than 1 000 mg Al per kg dry weight in their leaf tissues should be termed hyperaccumulators [75]. Hyperaccumulators may use Al in their tissues to deter herbivory, similar to other metals that are hyper-accumulated by plants. In support of this hypothesis, Al application prevented the herbivory of tall fescue (*Festuca arundinacea*) [76]. While toxic at high levels, Al has been shown to be beneficial to some plant species when supplied at low concentrations increasing antioxidant activity. It is known that tea bush can accumulate large quantities of Al in its leaves, from 8 700 to 23 000 mg kg^{-1}, and even up to 30 000 mg kg without experiencing Al toxicity [77]. Under Al stress, the leaf antioxidant defence system can scavenge excessive ROS and sufficiently protect itself from free radical injury.

Plant cells are equipped with a defensive system composed of enzymatic antioxidants such as catalase (CAT), ascorbate peroxidase (APX), guaiacol peroxidase (GPOX), superoxide dismutase (SOD), monodehydroascorbate reductase (MDHAR), dehydroascorbate reductase (DHAR), glutathione-S-transferase (GST), and gluthatione reductase (GR) and non-enzymatic antioxidants such as ascorbate (AsA), glutathione (GSH), α-tocopherol, and carotenoids that help to detoxify the ROS potentially caused by Al [78–82]. The Table summarises plant resistance mechanisms to Al toxicity.

Table. **Resistance to aluminium mechanisms in plants (catalase (CAT), ascorbate peroxidase (APX), guaiacol peroxidase (GPOX), glutathione-S-transferase (GST), dehydroascorbate reductase (DHAR), superoxide dismutase (SOD), monodehydroascorbate reductase (MDHAR), gluthatione reductase (GR))**

Detoxification Mech.	**Exclusion**							**Compartmentalization**			**Tolerance**	
Strategy	Reducing mobility	Reducing bioavailability		Exudation				Storing less toxic Al compounds		Limited transloc. from roots to shoots	ROS detoxification	
Method	Binding of Al	Complexing Al by exudations	Raise proximal soil pH	Complexing Al with organic acid anions				Chelation of cyt. Al and storing in vacuale		Immobilization of Al by P in roots	Enzymatic antioxidants	Nonenzymatic antioxidants
Compartment	Apoplast/ Cell wall	Apoplast	Apoplast	Apoplast and symplast				Symplast		?	Symplast	Symplast/ Apoplast
Site/Tissue	Root	Root	Root		Xylem sap	Root		Vacuale	Xylem paren-chyma cells	roots	Non. Spec.	Non. Spec.
Active compounds/ proteins	Nega-tively char. carboxylic groups of pectic matrix	Organic acids mucilage		Malate	Citrate	Oxalate	Pyruvate, and/or succinate	Various organic acids anionic complex ($Al(O_{x3})^{3-,}$)	Cytrate (Al(Cit) n-anionic complex)	P	CAT, APX, GPOX, GST, DHAR, SOD, MDHAR, GR	Ascorbate, Glutathione , α-tocopherol, Carotenoids
Transporters				Malate transporter ALMT	Citrate transporter MATE		Organic-anion-perme-able PM channels				-	-
Reference	Horst et al., 2010 [64]	Horst et al., 2010 [64]	Horst et al., 2010 [64]	Sasaki et al., 2004 [66]	Ma, 2007 [62], Liu et al., 2009 [69]	Morita et al., 2008 [71]	Sasaki et al., 2004 [66])	Klug and Horst, 2010 [65]	Klug and Horst, 2010 [65]	Liao et al., 2006 [73]	Martins et al., 2013 [79] Sun et al., 2014 [81]	Ribeiro et al., 2012 [80] Radic et al., 2010) [82]

Bioavailability of Al in human everyday life

Everyday life exposure to Al is very difficult to determine due to the wide range of exposure sources and time spent interacting with them. One of the most important sources of Al for an average citizen is food. Al can arise from contact with Al used in food containers, cookware, utensils and wrappings. Aluminium in food can derive from that which is present naturally. Tea, some spices and herbs (e. g. thyme, cayenne powder) contain naturally high aluminium concentrations. But mostly it can result from aluminium-containing food additives. For example, acidic sodium aluminium phosphate was present in many food products, pancakes and waffles. Baking powder, some pancake/waffle mixes and frozen products, and ready-to-eat pancakes provided the most Al of the foods tested: up to 180 mg/serving. Many products provide a significant amount of Al compared to a typical intake of 3–12 mg/day reported from dietary Al studies conducted in many countries [83].

Aluminium salts are currently utilized as anticaking agents for baked goods, to emulsify cheese, bind meats, thicken prepared sauces, colour desserts, buffering, stabilizing, curing, and giving texture to foods [5]. Aluminium additives in the forms of aluminium chloride, aluminium citrate, aluminium maltolate, other aluminium-food acid complexes, aluminium phosphate, aluminium silicate, aluminium sulfate and other aluminium species enter our body every day [36]. So it is difficult to monitor the extent of everyday aluminium exposure.

Other aluminium source comes from salts which are widely used in water purification as coagulants purposes to reduce organic matter, turbidity, and microorganisms as well as in brewing and sugar refining [84]. Flocculation by the most commonly used Al sulfate frequently increases the levels of the more toxic soluble monomeric inorganic forms in the finished water. Of significant concern is the presence of potentially extremely toxic fluoroaluminates (AlF–x), which form in aqueous solutions containing fluoride anions and trace amounts of Al [85]. Although the use of aluminium hydroxide is no longer recommended in dialysis units, aluminium, given its high potency binding to phosphate, is still being used in clinical practice with limitations [86], but the risk of aluminium overload is not restricted to subjects affected by chronic kidney diseases undergoing dialysis: general populations may be exposed to aluminium toxicity when aluminium sulfate is used as a sedimentation agent for treating city water [1].

Al can also be present in many pharmaceuticals such as antacid which can raise Al ingestion to several grams on a daily basis. Buffered aspirin containing aluminium glycinate has been used as a common analgesic for years [8].

It is assumed that ingested aluminium is not absorbed, or any small amount of aluminium absorbed would be removed by the kidneys. ^{26}Al and accelerator mass spectrometry studies have provided clear evidence that small amounts of dietary aluminium are routinely absorbed across the gastrointestinal tract lining and into the blood. About 2×10^{-6} and 4×10^{-8} of ingested Al is permanently (within 30 days of experiment) deposited in the liver and brain of rats, respectively [87]. Flarend et al. demonstrated the unequivocal absorption of aluminium across the skin [88]. So if Al is also found in topically applied cosmetics, especially sunscreens and antiperspirants, absorption across the skin occurs in everyday life. Application of aluminium-based antiperspirant salts, aluminium chloride, aluminium chlorhydrate, aluminium zirconium chlorhydrate glycine complexes to the underarm does constitute a specific high exposure level for the breast region [89]. A study has highlighted the ability of Al chloride to pass through the skin in significant quantities and its excretion in urine [90].

Aluminium-based adjuvants (ABA) are the predominant adjuvants used in human vaccinations. In vaccination and allergy treatment, up to a milligram of Al can be injected along with an antigen or allergen [91]. The most common Al compounds used in biological products to enhance the immune response are aluminium potassium sulphate (alum), aluminium hydroxide and aluminium phosphate [92].

Another route of the entry of aluminium to the brain is the olfactory system and the movement of originally airborne aluminium directly into the hippocampus. Although tobacco is rich in Al smoking is a potential source of Al to the body. Active and passive smoking of tobacco or cannabis will increase the body burden of aluminium [93]. Sources of aluminium in human everyday life are summarized in Fig. 1.

Human health problems related to aluminium overload

Usually in everyday life organisms are not exposed to the levels of biologically available aluminium, which are responsible for immediate acute toxic effects. Aluminium accumulates over time within a particular compartment – a cell or tissue – until achieve some threshold dose. A lack of symptoms which are immediately recognizable as aluminium toxicity relates to the biological reactivity of Al^{3+}(aq) and its significant propensity to be bound by oxygen-based functional groups associated with myriad biomolecules [45]. The potential for aluminium to interact with and to influence so many biochemical pathways means that the symptoms of its toxicity are scattered. One of Al characteristics is that it produces biphasic effects in cells: initially stimulating various activities and, when cells have accumulated sufficient aluminium levels, inhibiting the same activities.

Al is a known pro-oxidative, cytotoxic, neurotoxic, immunogenic, pro-inflammatory and mutagenic agent [3]. Figure 2 summarizes the main cellular targets affected by aluminium and aluminium related diseases.

Normally approximately 95% of an aluminium load becomes bound to the iron transport protein transferrin and albumin intravascularly, but the strength of binding is low and the metal is readily removed from blood in the kidneys and is then eliminated renally. When the gastrointestinal barrier is

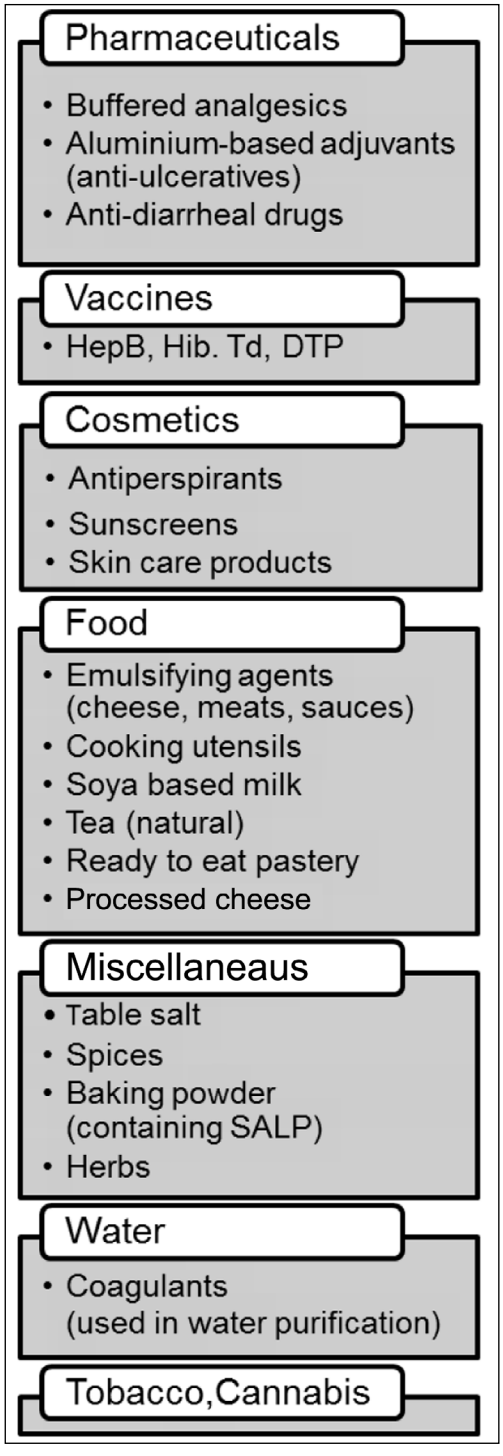

Fig. 2. Main sources of aluminium consumption

bypassed (such as by intravenous infusion or in the presence of advanced renal dysfunction), aluminium has the potential to accumulate. As a consequence of the retention of some aluminium, it is predicted that aluminium body-burdens will increase as a function of time. Aluminium toxicity is usually found in patients with impaired renal function [45].

Aluminium has been associated with several human diseases, such as dialysis encephalopathy [94], amyotrophic lateral sclerosis and Parkinsonism dementia complex of Kii peninsula and Guam [95] renal osteodystrophy [34], anemia [96], Alzheimer's disease [36], breast cancer [89] and autoimmune (auto-inflammatory) syndrome induced by vaccination 97].

Data reveals the effect of Al on the mail reproductive system. In particular mechanisms involving reactive oxygen species and oxidative damage have been highlighted as well as endocrine disruption of testosterone production, androgen receptor expression and libido decrease [98].

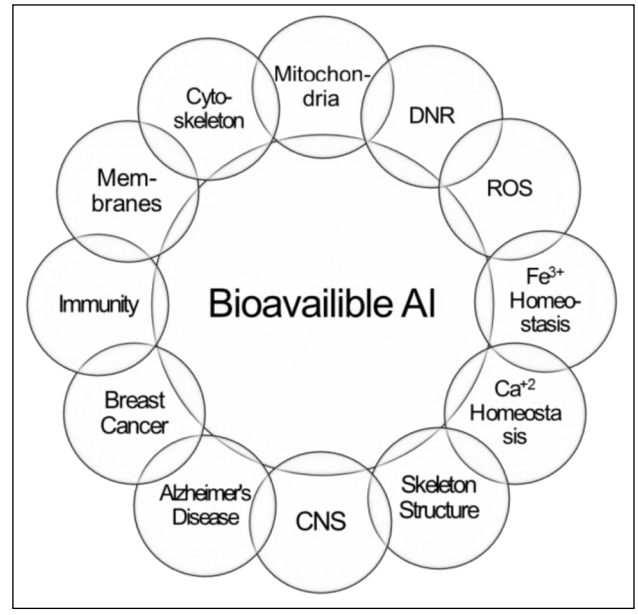

Fig. 3. Main cellular targets effected by aluminium and aluminium related diseases

CONCLUSIONS

Aluminium due to its complex chemistry is characterized by highly variable bioavailability. Aluminium targets the most important cellular processes: Al interferes with DNA, Ca^{2+} and Fe^{3+} homeostasis, cytoskeleton, membrane properties and generates ROS, altogether affecting human disease occurrence and influencing plant growth. From the evolution point of view it appears that Al^{3+} was not allowed to enter the cell. It seems that the best solution for the humans in the case of "Aluminium age" is to avoid all aluminium-containing antacids, antiperspirants, dialysate, immunizations, and Al in the parenteral nutrition. This solution seems simple, but it appears not always convenient. Scientists learned to control acute Al toxicity, but as characteristics of Al toxicity are complex, we need to realize the danger of accumulative long-term Al exposure. Aluminium should be recognized as a dangerous compound and should be accounted for in various treatments. As an example, a modern reverse osmosis approach should be employed to produce aluminium free water for risk patients and neonates. There is a real need for treatments, which will facilitate the removal of aluminium from the body and,

preferably, without affecting essential metals, such as iron. Al toxicity and plants as a source of aluminium should be considered when developing genetically modified crop species and pursuing agricultural practices on acidic soils. There is a vast amount of researches and data about bioavailable aluminium excess and related diseases; however, a limited public awareness and actions regarding aluminium danger remain.

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Vilma Kisnierienė, Indrė Lapeikaitė

ALIUMINIS CHEMIJOS IR BIOLOGIJOS SANKIRTOJE: APŽVALGA

S a n t r a u k a

Aliuminiui būdingos ypač sudėtingos cheminės savybės, lemiančios didelę neorganinių ir metaloorganinių kompleksų įvairovę, pasižyminčią kintamu stabilumu tirpaluose. Būdamas labai reaktyvus Al gali reaguoti su daugeliu biomolekulių bei daryti įtaką biocheminiams keliams, ląsteliniams procesams ir fiziologinėms funkcijoms. Aliuminio toksiškumas lemiamas ne tik tirpaus Al koncentracijos, bet taip pat cheminės formos, kuri labai priklauso nuo tirpalo pH ir cheminės sudėties. Al oksidacinis potencialas sukelia oksidacinį stresą, kuris paaiškina dalį aliuminio toksiškumo mechanizmų. Al pasižymi prooksidacinėmis, citotoksinėmis, neurotoksinėmis, imunogeninėmis, uždegiminėmis ir mutageninėmis savybėmis. Itin pavojingas aliuminio kaupiamasis poveikis per ilgą laiką gali sukelti keletą ligų ar sutrikdyti augalų augimą. Tačiau augalai, skirtingai nei gyvūnai ar žmonės, per evoliuciją išvystė mechanizmus, padedančius priešintis aliuminio stresiniam poveikiui. Šiame straipsnyje apžvelgiamos cheminės Al savybės, jo biologinis prieinamumas, gyvūninių bei augalinių ląstelių atsakai bei sutrikimai, nulemti Al toksiškumo. Netipinė Al chemija *in vivo* ir biologinių procesų sudėtingumas reikalauja kompleksinių tarpdisciplininių tyrimų, padėsiančių rasti geriausius sprendimus kovojant su Al toksiškumu ir šalinant jį iš organizmų.