Aluminum and Human Health: Its Intake, Bioavailability and Neurotoxicity

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Abstract

Aluminum (Al) is the 3rd abundant element in the earth’s crust. However, it is not essential for life. Owing to its specific chemical properties, aluminum inhibits more than 200 biologically important functions and causes various adverse effects. It is suggested that the exposure to aluminum has a relationship with neurodegenerative diseases including dialysis encephalopathy, amyotrophic lateral sclerosis, and Parkinsonism dementia in the Kii Peninsula and Guam, and Alzheimer’s disease. However, these relationships still remain elusive. Furthermore, the complexity of bioavailability has difficulty in evaluation of aluminum toxicity. In this paper, we review the detailed characteristics of aluminum neurotoxicity and bioavailability based on the recent literatures, and discuss its biological fate and effects to human health. Considering its long half-life in the body, unnecessary exposure to aluminum should be avoided for human health.

Keywords: bioavailability, gastrointestinal absorption, contamination, apoptosis

1. Introduction

Aluminum (Al) is the 3rd abundant element in the earth’s crust and is wildly distributed in our environment. Al is highly reactive and does not exist as a free metal in nature. Therefore, daily use of Al as a silvery metal was developed only after 1886, although Al compounds with other elements such as oxygen, or silicon such as Alum has been used from centuries ago. Nowadays, Al metals and compounds are widely used in various important industrial applications or in consumer products such as antacids, food additives, and antiperspirants. In spite of its abundance, Al is not an essential element and there are no known reactions which require Al. On the contrary, Al is toxic to most life beings because of its peculiar chemical properties. Al eluted from soil under low pH conditions in acid rain causes toxicity to plants and fishes etc. Al has been suspected with various diseases such as aluminum bone disease, encephalopathy in dialysis patients. In particular, the link between Al and neurodegenerative diseases such as Alzheimer’s disease has been suspected for decades; however, it remains still elusive. Its daily intake and bioavailability are still under investigation because of the lack of proper radioisotopes. In this paper, we review the biological fate of Al and its neurotoxicity based on the recent findings.

2. Chemical property of aluminum and its toxicity

Al has several specific chemical characteristics. Al exhibits only one oxidation state, Al³⁺. Al³⁺ favors negatively charged, oxygen-donor ligands. Inorganic or organic phosphates, carboxylate, deprotonated hydroxy groups firmly bind to Al³⁺. Thus, Al³⁺ binds to the phosphate groups of DNA or RNA, influences DNA topology, and affects gene transcription. Lukiw et al. reported that nanomolar level of Al³⁺ was enough to bind...
to DNA and to influence neuronal gene expressions. 

Al\(^{3+}\) also binds to the phosphate groups of nucleoside di- and triphosphates, such as adenosine triphosphate (ATP) and affects energy metabolism. Also, Al influences various functions of enzymes including protein kinases and phosphatases. Al\(^{3+}\) has similar characteristics to Fe\(^{3+}\), and binds to iron-binding protein such as transferrin. Therefore, Al\(^{3+}\) affects iron-homeostasis and the substitution of Al\(^{3+}\) in iron responsive protein (IRP) could influence the expression of various proteins with iron responsive element (IRE). Although Al\(^{3+}\) does not directly affect the peroxidation, Al\(^{3+}\) stimulates iron-induced lipid peroxidation and causes oxidative damages.

Furthermore, the ligand-exchange rate for Al\(^{3+}\) is very low compared with those for other essential elements. For example, the ligand-exchange rate of Mg\(^{2+}\) is 10\(^5\) times faster than Al\(^{3+}\), and therefore, Al\(^{3+}\) inhibits enzymes with Mg\(^{2+}\) cofactors. Biological processes involving a rapid Ca\(^{2+}\) exchange could be inhibited by the substitution with the 10\(^8\)-fold slower Al\(^{3+}\) exchange. These properties enable Al to become useless in enzymerequiring reactions, and to have the long half-life in the body. Accordingly, Al is reported to affect more than 200 biologically important reactions. They include numerous crucial reactions for brain developments such as the axonal transport, neurotransmitter synthesis, phosphorylation or dephosphorylation of cytoskeleton proteins, protein degradation, and neuronal apoptosis. Table 1

**Table 1** Effects of aluminum on the central nervous system*

<table>
<thead>
<tr>
<th>1. Effects on nucleas and gene expression</th>
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<tbody>
<tr>
<td>* binds to histone-DNA complex and induces conformational changes of chromatin</td>
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<td>* induces topological changes of DNA</td>
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*Altered gene expression* |
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<tr>
<td>* induces decreased expression of neurofilament, tubulin</td>
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<tr>
<td>* induces altered expression of neurofilament, APP, and neuron specific enolase</td>
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<tr>
<td>* induces decreased expression of transferrin receptor</td>
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<td>* induces altered expression of RNA polymerase I</td>
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<td>* induces down regulation of mitochondrial cytochrome c oxidase</td>
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<tr>
<td>* alters the expression of calbindin-D28k</td>
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<td>* induces decrease in the expression of nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF)</td>
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<th>2. Effects on cellular functions</th>
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*Energy metabolism* |
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<tr>
<td>* inhibits the activity of hexokinase</td>
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<td>* inhibits the activity of phosphofructokinase</td>
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<td>* inhibits the activity of glucose-6-phosphate dehydrogenase</td>
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*Phosphorylation* |
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<td>* inhibits the activity of protein phosphatase</td>
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<td>* increases the activity of protein kinase C and phosphorylation of MAP2 and neurofilament</td>
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<td>* inhibits dephosphorylation of tau</td>
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<td>* induces non-enzymatic phosphorylation of tau</td>
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<td>* activates of cAMP-dependent protein kinase</td>
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*Cytoskeleton protein* |
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<td>* accelerates phosphorylation and accumulation of neurofilament</td>
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<td>* accelerates phosphorylation of MAP 2 and neurofilament 200kD</td>
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<tr>
<td>* causes aggregation of MAP1A, MAP1B, neurofilament200kD, 160kD</td>
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<td>* accelerates phosphorylation and accumulation of tau</td>
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summarizes the major toxic reactions of Al in the central nervous system.

Neurotransmitter release

- inhibits glutamate release
- impairs glutamatergic neurotransmission
- inhibits choline acetyl transferase and tyrosine hydroxylase, glutamate decarboxylase, activates monoamine oxidase
- inhibits dopamine β-hydroxylase
- inhibits uptake of serotonin and noradrenalin in synaptosomes
- inhibits synaptic transmission

Others

- influences the activities of Na⁺ channels and K⁺ channels
- inhibits GAP junction
- inhibits axonal transports
- binds to calmodulin and inhibits calmodulin-binding enzymes
- activates alpha-ketoglutarate dehydrogenase and succinate dehydrogenase
- inhibits aconitase, glutamate dehydrogenase

3. Effects on cellular membranes

Peroxidation of membrane lipids

- accelerates iron-induced membrane lipid peroxidation
- induces peroxidation of myelin lipids

Membrane properties

- causes the change the lipid/phospholipids profiles in myelin
- induces the change in membrane physical properties (surface potential, lipid fluidity, and lipid arrangement)
- induces the change of membrane fluidity

4. Pathological changes related to Alzheimer’s disease

- causes the accumulation of β-amyloid protein in vitro and in vivo
- causes the accumulation of tau protein
- causes neurofibrillary degeneration

5. Effects on higher functions of brain

Cell death

- causes the apoptotic neuronal death
- causes the apoptosis of astrocytes
- causes the death of motor neuron

Behavior, learning, and memory

- inhibits long term potentiation (LTP)
- causes epilepsy
- causes learning disorder
- impairs spatial working memory
- causes encephalopathy

* modified from reference No. 7.

3. Link between aluminum and Alzheimer's disease

3-1. History

Owing to these chemical characteristics, Al is toxic to most life beings. In humans, a case of Al poisoning
Aluminum hypothesis is still controversial and has been the subject of debate over several decades. There were arguments that NFTs in Al-intoxicated animals (Al-NFTs) are different from those in AD patients (AD-NFTs) because of several morphological and biochemical differences, and that there is no significant difference in the levels of Al between AD patients and age-matched controls, and the aluminum hypothesis has been the subject of much debate during these several decades. However, there is increasing evidence countered these arguments. Properties of Al-induced neurotoxicity in vitro as well as in vivo have demonstrated the similarity between AD’s pathological hallmarks, accumulation of AβP and tau protein. Savory et al. reported that depositions in the brains of Al-intoxicated animals were immunostained with the anti-tau antibody that recognizes PHF-tau in the AD brain. The accumulation of the tau protein in patients with dialysis encephalopathy was observed. We have demonstrated that the chronic application of Al causes the accumulation of the tau protein and AβP in cultured neurons of rat cerebral cortex. Moreover, the recent findings of Pratico et al. have demonstrated that Al-fed mice transfected with the human APP gene exhibited pathological changes similar to those of the AD brain, such as the marked increase in the amount of both secreted and accumulated AβP. The increased deposition of senile plaques was also observed. Furthermore, recent findings about the case study of accidental Al-exposure occurred at 1988 in Camelford (Cornwall, U.K.) revealed that short-term exposure of Al could cause adverse effects of human. Neuropathological study of a 58-year woman who was exposed to Al and died after 15 years later with neurological symptoms demonstrated the rare form of cerebral amyloid angiopathy and the highly deposition of Al in the patient’s brain. These new lines of evidence counter the arguments about aluminum hypothesis and make it difficult.

3-2. Arguments about aluminum hypothesis and the counter-arguments

Although the etiology of AD remains elusive, genetic and toxicological studies have support the idea that the accumulation, the conformational changes, and the neurotoxicity of AβP have the causative role in the pathology of AD. AβP is a small peptide with 39-43
4. Intake of aluminum and its bioavailability

4-1. Daily intake of aluminum

As far as we concern, Al causes dementia when enters into the brain even if the link between AD is controversial. Therefore, the amount of Al is crucial as to our health.

Most of our daily intake of Al is from food stuffs. Several plants or weeds originally hold Al in the body. Usually the levels of Al in most foodstuffs are low and varied within a wide range. Meanwhile, the contamination from food additives or from cooking utensils accounts for a large part of its intake. Thus, our daily intake of Al was estimated to be 10-20 mg/day.[30-40] National Food Administration in Sweden reported in 1992 that Swedish daily intake of Al was estimated to be 13 mg[41]. Baking soda was identified the most important contributor. Aluminum utensils were estimated to increase the Al contents by approximately 2 mg/day. Al is used as coagulants of water treatment process, and therefore, drinking water contains Al. Furthermore, much amount of Al is included in medicines such as antacids or antiperspirants. WHO recommended the value for acceptably weekly intake of Al as less than 7 mg/kg. This means an adult of 60 kg can consume a diet containing up to 60 mg/day without exceeding this intake.

4-2. Bioavailability of aluminum

In general, Al intake does not correlate with the amount of Al in the body. In general, metals including Al consumed can be adsorbed by gastrointestinal tract, but the ratio is low and widely varied. Thus, the bioavailability of Al, namely, the amounts of Al that are absorbed in the gastrointestinal tract, transported into the brain through blood brain barrier, and accumulated in the brain are crucial for our health. Although the lack of proper radioactive isotopes of Al had prevented the research of Al bioavailability, recent developments of acceleration mass spectrometry using 26Al have advanced the research. Usually, small amount of Al (approximately less than 1%) is absorbed from food via the gastrointestinal pathway[46-50]. However, the uptake of Al through gastrointestinal pathway is complex and is influenced by various factors including an individual difference, age, pH, stomach contents, chemical speciation of Al, coexistence substances. For example, Al hydroxide (Al(OH)₃), a main component of antacids is much less absorbed compared to Al citrate[51]. The coexistence of organic ligands such as citric acid or...
maltol promotes the absorption of Al, while silic acid prevents it. Although the consumption of tea contributes much in the daily intake of Al, Al in tea infusion is less adsorbed. It is possible that Al eluted from cooking utensils is highly bioavailable because the discontinuation of the use of Al-utensils decreased the serum Al levels. The rate of Al absorption is increased in aged people, in patients with Down’s syndrome, patients with AD. The amounts of Al become high in bodies of patients with renal failure or kidney disease.

**Fig. 1** Hypothesis regarding the implications of Al and other trace metals in the pathogenesis of Alzheimer’s disease.

Here described the implication of Al and other trace metals including Fe, Cu, and Zn. Al binds to IRP and influences the expression of proteins with IRE such as ferritin as well as Fe. APP has IRE, and therefore, it is possible that Al causes the abnormal expression of APP and finally leads to the increased amount of AP. Normally secreted AP is degraded by various proteases. However, AP which is aggregated in the presence of trace metals, including Al, Zn, Fe, and Cu, could be resistant to proteases and accumulates in the brain. Therefore, it is possible that Al causes the increased amount of both secreted AP and accumulated AP. AP could be incorporated into membranes resulting in the formation of ion channels. The abnormal calcium influx through amyloid channels cause the phosphorylation of tau, the depletion of neurotrophic factors such as brain derived neurotrophic factor (BDNF), and the formation of free radicals, and finally induces neuronal death. Al implicates these neurodegenerative pathways by inhibiting of BDNF-induced increase in intracellular calcium levels, by accelerating the phosphorylation of tau, and by stimulating iron-induced lipid peroxidation. Meanwhile, abnormal expression of ferritin induced by iron dyhomeostasis will cause an altered concentration of free iron ions, and thus, will lead to oxidative damage and membrane lipid peroxidation. All of these events finally lead to neuronal death. It is possible that Al and other metals are implicated in various stages of these degenerative processes and finally link to the pathogenesis of Alzheimer’s disease (modified from Ref. No. 7).
Once absorbed from the gastrointestinal tract, Al rapidly appears in the blood and approximately 80% of Al is transported with binding to transferrin, iron transporter protein \(^{48}\). The rest of Al binds to albumin and citrate in the serum. About half of Al in the serum is excreted in the urine through kidney. Rest is accumulated in the bone. Small, but considerable amount of Al can cross the blood brain barrier maybe through transferrin-receptor pathway or monocarboxylate transporters, and enters into the brain \(^{49,50}\). Once entered, Al retains in the brain and accumulated permanently. Kobayashi et al. reported that intraperitoneally or orally administered \(^{26}\)Al was transferred to the brain and the amount of Al in the brain is not changed after 35 days, although Al in the serum disappeared rapidly \(^{51}\). Thus, it is possible that the ability to eliminate Al from brain is very low. These results are coincident with the findings that the amount of Al in the brain is increased in age-dependent manner although other trace elements are not \(^{52}\). Figure 2 summarizes the biological fate of Al from the various sources.

**Neurotoxicity of Aluminum**

Daily intake of Al from foods is estimated to be 10-20mg derived from intrinsic foodstuffs, contamination by food additives or utensils, etc. Although the intake from antacids will contribute much more, its absorption rate is usually low in healthy adults. However, antacid could cause adverse effects in dialysis patients or patients with kidney failures. In general, gastrointestinal absorption rate is approximately 1%. However, it is different in each individual, and largely influenced by age, pH, stomach contents, chemical speciation of Al, coexistence substances such as silic acid. Meanwhile, Al in the dialysis solution or in TPN solution could be easily absorbed and will contribute more to total amount of Al in the body. Once entered in the blood flow, approximately 50% of Al in the plasma is excreted from kidney. However, rest is accumulated in the skeletons permanently. Furthermore, small but considerable amount of Al passes through blood brain barrier and enters into the brain. Al in the brain is almost not excreted and accumulated through lifetime. Values of the absorption rate are obtained from Ref. No. 49.

Once absorbed from the gastrointestinal tract, Al rapidly appears in the blood and approximately 80% of Al is transported with binding to transferrin, iron transporter protein \(^{48}\). The rest of Al binds to albumin and citrate in the serum. About half of Al in the serum is excreted in the urine through kidney. Rest is accumulated in the bone. Small, but considerable amount of Al can cross the blood brain barrier maybe through transferrin-receptor pathway or monocarboxylate transporters, and enters into the brain \(^{49,50}\). Once entered, Al retains in the brain and accumulated permanently. Kobayashi et al. reported that intraperitoneally or orally administered \(^{26}\)Al was transferred to the brain and the amount of Al in the brain is not changed after 35 days, although Al in the serum disappeared rapidly \(^{51}\). Thus, it is possible that the ability to eliminate Al from brain is very low. These results are coincident with the findings that the amount of Al in the brain is increased in age-dependent manner although other trace elements are not \(^{52}\). Figure 2 summarizes the biological fate of Al from the various sources.

4-3 Iatrogenic exposure of aluminum

Al in the medicinal usages is more crucial to our health because of its bioavailability. As noted, the gastrointestinal absorption of Al is low compared the
iatrogenic absorption such as from the dialysis solution. For example, considerable amount of Al is contaminated in total parenteral nutrition (TPN). Al in TPN solutions is completely absorbed, enters into the blood flow. Although a part of Al in the blood is excreted from the kidney, the problem is some patients receiving TPN solutions have the failure in kidney functions. In particular, the kidney functions of infants are not perfect. The accumulation of Al in bones of patients receiving TPN was reported. Bishop et al. reported that preterm infants received TPN containing high concentration of Al had a lower score on mental development than age-matched infants received TPN with low Al\(^{53}\). Based on these findings, The U.S. Food and Drug Administration (FDA), the North American Society for Pediatric Gastroenterology and Nutrition, and other societies have recommended the reduction of the contamination of Al in TPN solutions\(^{54}\). FDA published the final rule requiring to be labelled the concentration of Al in TPN at 2000. The rule was delayed but effective from 2003. The method for determination of Al in TPN was also added in the 15\(^{th}\) Japanese Pharmacopoeia. Furthermore, huge amount of Al is included in antacids, and therefore, the continuous exposure of Al-containing antacids to patients with renal failure or kidney diseases may increase the risk of encephalopathy. The Japanese Ministry of Health, Labour and Welfare recommended that patients on dialysis or with kidney failure should not use Al-containing antacids.

Another source of Al for infants is from milk. Al is highly contaminated in infant formulas\(^{55}\). Yumoto et al. demonstrated that \(^{26}\)Al administered to mother rats was transported to the brain of suckling infants through maternal milk\(^{56}\). The amount of \(^{26}\)Al was not changed through the lifetime of the infant rats. Considering that the development of complex brain networks are accomplished during the infant stage, Al may cause some adverse effects in our brain development.

5. Conclusion

It is widely accepted that Al is a neurotoxin, and could cause cognitive deficiency and dementia when Al enters the brain. In particular, Al can affect infants, elderly people, and patients with impaired renal functions, and can cause severe health problem. Therefore, unnecessary exposure to Al should be avoided for such patients. Further detailed researches on the neurotoxic characteristics of Al, including its bioavailability, cellular effects, metabolisms, and in particular, metal-metal interactions are required.

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