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Neurotoxicity of aluminum and its link to neurodegenerative diseases

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Abstract

Aluminum (Al) is the third most abundant element in the earth's crust. However, because of its specific chemical properties, Al is not essential for life, and it exerts various adverse effects on plants, animals, and humans. In particular, Al is a widely recognized neurotoxin. The association between Al and neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis and Parkinson's disease dementia in the Kii Peninsula and Guam has been suspected. However, controversy has persisted for several decades. Based on recent epidemiological, analytical, and toxicological studies, we review the detailed characteristics of Al neurotoxicity and revisit its link to Alzheimer's disease and other diseases. The daily intake of Al and its bioavailability linked with adverse effects on human health are also described.

Key words: aluminum, Alzheimer's disease, bioavailability, iron, neurotoxicity

Statements about COI: All authors declare that there are no conflicts of interests.

1. Introduction

Aluminum (Al) is the third most abundant element in the earth's crust and is widely distributed throughout the environment. Materials containing Al (*e.g.*, clay, glass, and alum) have been used for centuries. In this context, Al is considered to be an old and well-known metal. However, Al was first isolated as an element in 1827, and its use as a silvery metal began only after 1886. Because Al is light, nonmagnetic, malleable, and ductile, it has widespread and important uses in industrial applications and manufacturing of consumer products. From this perspective, Al is a new metal.

Al is widely distributed throughout the environment and eluted from soils by acid rain. Al can enter the human body through foods, cooking utensils, pharmacological agents (such as antacids, antiperspirants, medicine for hyperphatemia, and vaccines), occupational exposure such as use as a leather tanning agent, a component of hemodialysis solution and drinking water after purification with Al coagulants such as aluminum sulphate or polynuclear hydroxyaluminum chloride (PAC)[1].

Despite its widespread distribution throughout the environment, Al is not essential for life, and there is no known biological reaction that requires Al. In contrast, Al is a well-established neurotoxin. As a component of hemodialysis solution or pharmacological compounds, Al causes dialysis encephalopathy in hemodialysis patients[2]. In the environment, Al is eluted from soils by acid rain and

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causes toxicity to plants and fishes. Furthermore, Al has been linked to various neurodegenerative disorders including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Parkinson's disease dementia (PDD) in the Kii Peninsula and Guam, Gulf-war syndrome, and autism spectrum disorder (ASD)[3-6].

In particular, a crucial link has been established between Al and AD. AD was first reported in 1906 and now accounts for approximately 60% of senile dementia cases. The pathological hallmarks of AD are the deposition of β-amyloid protein (AβP) as extracellular senile plaques and the presence of phosphorylated tau protein in intracellular neurofibrillary tangles (NFTs)[7]. It has been suggested that the risk factors of AD are age, sex, family history, apolipoprotein E phenotype, head trauma, and Al exposure[8]. The hypothesis that Al is an environmental contributor to the pathogenesis of AD, termed the "aluminum hypothesis", was proposed in the 1960s based on various neurotoxicological, analytical, and epidemiological findings [9-12]. Despite these findings, the aluminum hypothesis has been the subject of much debate and criticism for several decades[13]. Great progress has been made in AD research and Al toxicology research during this period, particularly in epidemiological findings about drinking water contaminated with Al and occupational exposure of Al, accumulation of Al in the AD brain, implication of Al in the conformational changes of AβP, and characteristics of Al-induced neurotoxicity. Therefore, it is good time to review Al neurotoxicty, especially based on new findings.

In this review, we focus on the neurotoxicity of Al based on its chemical properties and revisit the significance of Al in the pathogenesis of AD. We describe the daily intake of Al and its bioavailability and association with human health, particularly in infants.

2. Chemical characteristics of Al and its effects on the central nervous system

Despite its environmental abundance, Al is not an essential element and has no known function that is crucial for living organisms. This may be because of several specific chemical characteristics of Al[14].

Al exhibits only one oxidation state, Al^{3+}. In acidic solutions with pH < 4, Al^{3+} exists as the soluble octahedral hexahydrate $Al(H_2O)_6^{3+}$. In neutral solutions, Al^{3+} forms an insoluble hydroxide, $Al(OH)_3$; thus, the concentration of free Al^{3+} under physiological conditions is usually very low. In alkaline solutions with pH > 9.6, Al^{3+} exists as the soluble tetrahedral $Al(OH)_4^-$. This chemistry suggests that a low level of Al is present in the seawater from the era when life first evolved. Indeed, the concentration of Al in the earth's crust, which is termed as the lithospheric abundance of Al, is 82,000 ppm[15]. Meanwhile, the concentration of Al in the human body, the biospheric abundance, is only 0.9 ppm. Thus, the biospheric/lithospheric ratio of Al (approximately 1.1×10^{-5}) is extremely low compared with that of other essential elements such as calcium (Ca: 0.35), iron (Fe: 1.5×10^{-3}), and zinc (Zn: 0.44).

Al^{3+} has affinity for negatively charged, oxygen-donor ligands and strongly binds to inorganic and organic phosphates, carboxylate, and deprotonated hydroxyl groups. By this mechanism, Al^{3+} can bind to DNA and RNA and influence the expression of various genes such as those coding for neurofilament, tubulin, neuron specific enolase, mitochondrial cytochrome oxidase, nerve growth factor, and brain derived neurotrophic factor (BDNF)[11,16]. Lukiw *et al.* reported that nanomolar levels of Al^{3+} were sufficient to influence neuronal gene expression[17]. Al^{3+} also binds to the phosphate groups of nucleoside di- and triphosphates, such as ATP, and inhibits hexokinase, phosphofructokinase, and glucose-6-phosphate dehydrogenase[18], and therefore, Al^{3+} influences energy metabolism. Al also influences the functions of other protein kinases and phosphatases such as protein kinase C and Ca^{2+}/calmodulin-dependent protein kinase[11,19]. Interestingly, Al inhibits dephosphorylation of tau, the main component of AD-NFTs[20].

Al^{3+} has a very low ligand exchange rate compared with other metal ions. For example, the ligand exchange rate of magnesium (Mg^{2+}) is 10^5 times higher compared with that of Al^{3+}, and that of Ca^{2+} is 10^8 times greater. Therefore, Al cannot participate in Ca^{2+}- or Mg^{2+}-related enzymatic reactions and inhibits numerous enzymes with Mg^{2+} and/or Ca^{2+} cofactors. Because of its low ligand exchange rate, Al has a prolonged half-life in the body. Once it enters the brain, Al is retained and semi-permanently accumulates.

Meanwhile, there have been studies suggesting that Al affects the synaptic transmission *via* the mechanism related to Ca^{2+}. It has been reported that Al^{3+} inhibits various enzymes that regulate neurotransmitter synthesis, such as catecholamine o-methyl transferase, tyrosine hydroxylase, dopamine β-hydroxylase, choline acetyl transferase, tyrosine hydroxylase, and glutamate decarboxylase[11]. Moreover, Al inhibits various ion channels and neurotransmitter receptors including sodium (Na^+) channels,

potassium (K^+) channels, voltage-gated Ca^{2+} channels, N-methyl-D-aspartate-type glutamate receptors, and receptors of catecholamine-related neurotransmitters[21]. By the inhibition of neurotransmitter synthesis and receptors including voltage-gated Ca^{2+} channels, Al^{3+} impairs synaptic transmission and Ca^{2+} homeostasis.

Al^{3+} has similar characteristics to Fe^{3+} and binds to Fe-binding proteins such as transferrin and Fe chelators such as deferoxamine. Therefore, Al^{3+} affects Fe homeostasis and Fe-induced expression of various genes containing iron responsive elements (IREs) in their mRNA. Furthermore, Al^{3+} stimulates Fe-induced lipid peroxidation and causes oxidative damage *in vitro* and *in vivo*[22,23]. Increasing evidence suggests that Al acts as a pro-oxidant and induces reactive oxygen species (ROS) production, although Al is a non-redox-active metal[24-27]. It is also notable that co-exposure to Al and 6-hydroxydopamine, a model compound of Parkinson's disease, enhanced the auto-oxidation-induced oxidative stress in brain mitochondrial preparations[28].

As mentioned above, Al has been used as a leather tanning agent for many centuries, since Al^{3+} strongly binds to proteins, causing cross-linking and finally inducing conformational changes. Because Al^{3+} has strong positive charges with a relatively small ionic radius compared with other metal ions (such as Ca^{2+}, Zn^{2+}, and Na^+), Al^{3+} firmly binds to metal-binding amino acids (histidine [His], tyrosine [Tyr], and arginine [Arg]) and phosphorylated amino acids. The strong binding of Al^{3+} to phosphorylated amino acids promotes the self-aggregation of highly phosphorylated cytoskeletal proteins such as neurofilaments and microtubule associated proteins. Furthermore, Al inhibits proteolytic degradation of AβP by cathepsin D[28]. Thus, Al induces the accumulation of AβP as well as cytoskeleton proteins including neurofilaments, tau, and microtubule associated protein 2. The details of this process are discussed in section 4-1.

Because of these chemical properties, Al^{3+} reportedly influences the expression of various genes crucial for brain function and participates in more than 200 biologically important reactions[9,11]. These include processes crucial for brain functions, such as axonal transport, synaptic transmission, phosphorylation or dephosphorylation of proteins, protein degradation, and inflammatory responses. **Fig. 1** summarizes the effects of Al on the central nervous system. Once Al passes through the blood brain barrier and enters the brain by binding with transferrin and/or citrate (Ctr), it induces various adverse effects. Al binds to the phosphates of DNA/RNA and inhibits expression of various genes. It also perturbs Fe homeostasis and affects Fe-related gene expression. Al influences numerous enzymes including kinases, phosphatases, and enzymes that require Ca^{2+} and/or magnesium Mg^{2+} as a cofactor. Al impairs mitochondrial energy producing pathways by binding to ATP and by inducing the generation of ROS. Al also induces endoplasmic reticulum (ER) stress. Furthermore, Al causes cross-linking of and conformational changes in proteins and finally induces the accumulation of proteins including AβP, neurofilaments, and tau.

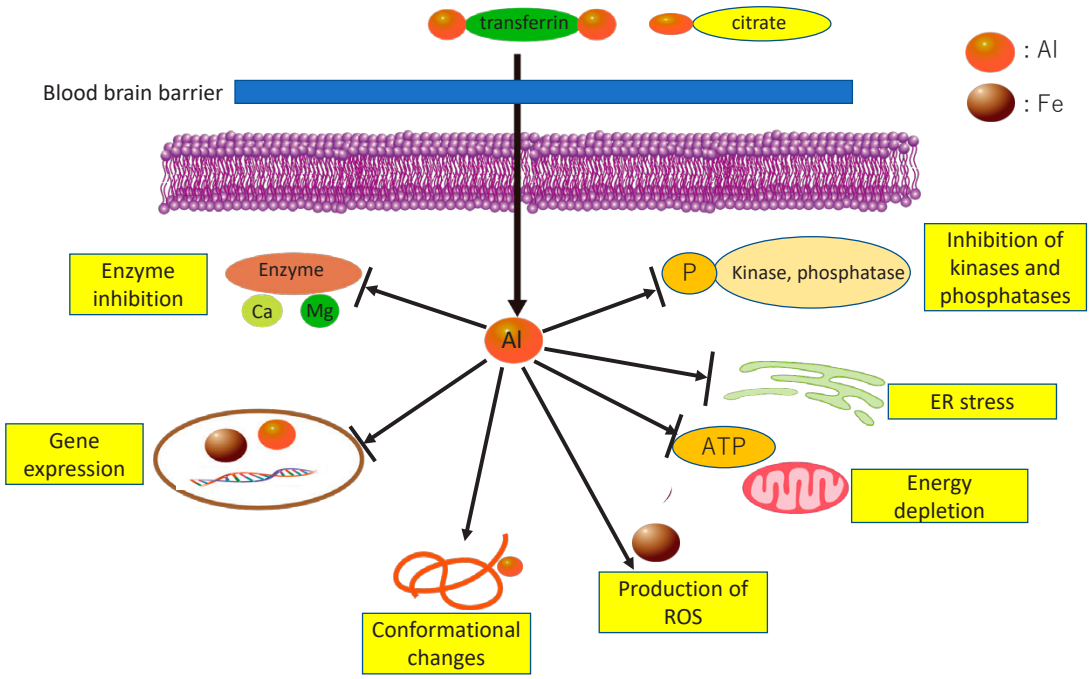

Fig. 1. **Effects of aluminum (Al) on the central nervous system.**
Al causes numerous adverse effects on the central nervous system. Details are shown in the text.

3. Neurotoxicity of Al

3-1. Al neurotoxicity *in vitro*

Because Al possesses these specific chemical characteristics, Al impairs various crucial neurological functions and eventually causes death of neurons and glial cells. We have reported that chronic application of $AlCl_3$ to primary cultured cortical neurons induced the accumulation of tau protein and AβP and the impairment of synapse formation, which are similar to the pathological changes observed in AD[30]. To explore the molecular mechanisms of Al neurotoxicity, its chemical speciation, namely, the types of ligands that coexist with Al and their concentrations, must be considered. The lability, stability, and hydrophobicity of Al compounds are dependent on the counterions because Al^{3+} easily forms insoluble $Al(OH)_3$ in aqueous solutions at physiological pH values[31].

Al binds to maltol (3-hydroxy-2-methyl-4-pyrone) and forms the hydrolytically stable complex termed aluminum maltolate ($Al(malt)_3$)[32]. It has been reported that the toxicity of $Al(malt)_3$ is higher than those of other Al compounds. We have examined the viability of primary cultured neurons after exposure to identical concentrations of four Al compounds, including the simple salt of Al^{3+} ($AlCl_3$), a relatively stable and hydrophilic complex (aluminum lactate ($Al(lac)_3$)), and two lipophilic Al species ($Al(malt)_3$ and aluminum acetylacetonate ($Al(acac)_3$)) [33]. $Al(acac)_3$ and $Al(malt)_3$ exhibited higher toxicity than $AlCl_3$ or $Al(lac)_3$. We have also demonstrated that $Al(malt)_3$ induced synaptic loss and death in primary cultured rat hippocampal neurons and that BDNF attenuated its toxicity[34]. $Al(malt)_3$ inhibits the increase in the intracellular Ca^{2+} level induced by BDNF, but it does not influence the increase in the intracellular Ca^{2+} level induced by KCl or glutamate[35]. Based on these results, it is possible that depletion of neurotrophic factors and disruption of Ca^{2+} homeostasis may be involved in $Al(malt)_3$-induced neuronal death.

$Al(malt)_3$ has been used as a convenient tool to investigate the molecular mechanisms of Al neurotoxicity. $Al(malt)_3$ reportedly causes apoptotic cell death by inducing an inflammatory response in neuronal cell model such as PC12 cells and SH-SY5Y cells[36]. $Al(malt)_3$ induces mitochondrial oxidative stress[37] and ER stress *via* PERK-Elf2a signaling pathway[38] in SH-SY5Y cells. Recent studies suggested that $Al(malt)_3$ also triggers non-apoptotic cell death including ferroptosis in PC12 cells[39] and necroptosis in SH-SY5Y cells [40].

Another crucial feature of the chemical speciation of Al is pH-dependent polymerization. As the pH increases, Al readily forms polynuclear hydroxy-Al complexes. In solutions at pH 5, aluminum tridecamer (Al_{13}; $[AlO_4Al_{12}(OH)_{24}(H_2O)_{12}]^{7+}$) is a dominant species[41], as shown in **Fig.2A**. In soils in which the pH has been decreased by acid rain, the eluted Al causes toxicity to plants and fishes. Al_{13} formed in the soil was reported to be more toxic to the growth of plant roots than monomeric Al^{3+} [42]. It is hypothesized that Al_{13} binds to the phosphate groups in the cell membrane and thereby inhibits various cellular functions[43]. Al_{13} has been shown to form in synaptosomes incubated under neutral pH conditions[44]. Al_{13} might exist in our environment, since polynuclear hydroxyaluminum chloride (PAC) is widely used in the water purification process in Japan[1].

We have developed a pulse-exposure method by which cultured neurons can be exposed to chemically-identified Al species[45]. Using ^{27}Al-NMR, we have confirmed that Al^{3+}, Al_{13}, and $Al(malt)_3$ are stable in 100 mM HEPES buffer (pH 7.0). Cultured neurons were exposed to solutions of monomeric Al^{3+}, Al_{13}, and $Al(malt)_3$ in this condition. After 1 h, the buffer was replaced with usual culture media, and the incubation was continued. At 14 days after the pulse exposure (200 μM for 1 h), Al_{13}-exposed neurons as well as $Al(malt)_3$-exposed neurons exhibited significantly decreased cell viability compared with those exposed to Al^{3+} (**Fig.2B**). Use of this technique with primary cultured neurons will provide a convenient tool to investigate the neurotoxicity of chemically-identified Al species.

3-2. Al neurotoxicity *in vivo*

Al also causes neurodegeneration in experimental animals and impairs various brain functions related to learning, memory, and behavior. Intracerebral administration of Al induces epilepsy in experimental animals, which have been used as models for epilepsy research [46]. Increasing evidence suggests that chronic administration of Al compounds in diets or drinking water causes various detrimental effects in experimental animals. Oral administration of $AlCl_3$ for 7 days caused neurobehavioral changes, increased oxidative stress, and decreased acetylcholine esterase and neurotransmitter levels of aged rats[47]. Exposure to $AlCl_3$ in drinking water caused long-term memory impairment and influenced BDNF gene expression in rats[48]. Al reportedly induces dendritic spine loss, ultrastructural changes in synapses, spatial memory deficits, and decreased emotional reactivity in rats [49,50]. Al also impairs long-term potentiation (LTP), which is a form of synaptic information storage and a paradigm of memory mechanisms in rats[51]. Zhang *et al.* demonstrated that chronic exposure to $AlCl_3$ in drinking water for 90 days caused

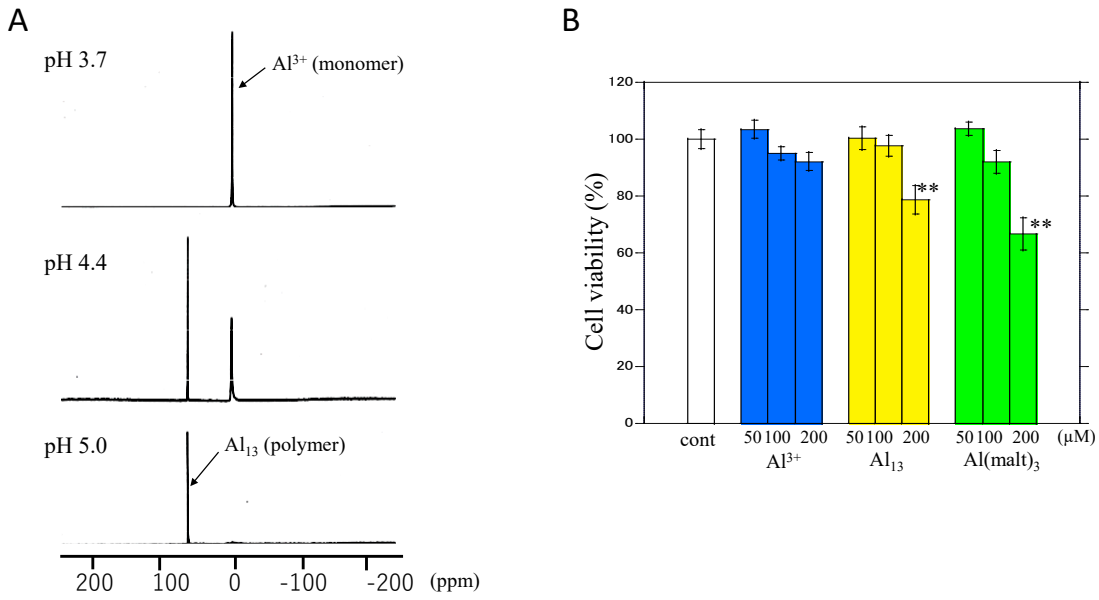

Fig. 2. **Chemical speciation of aluminum (Al) and its neurotoxicity**

A: ^{27}Al-nuclear magnetic resonance (NMR) spectrum of Al solutions at different pH values.
The NMR spectra of 10 mM solutions of Al at pH 3.7 (a), pH 4.4 (b), and pH 5.0 (c) were recorded using a GX-400 (Hitachi, Tokyo Japan). The standard peak (0 ppm) was adjusted according to $Al(NO_3)_3$. The arrow indicates the peak corresponding to Al_{13} at 63.5 ppm. The data are modified from Ref No.45 with permission.

B: The viability of cultured neurons after pulse-exposure to Al
After 14 days of pulse-exposure to 50–200 μM monomeric Al^{3+} (monomer), Al_{13}, or $Al(malt)_3$, the cell viability was examined using the WST-1 method. Data are expressed as means±SEM. * $p<0.05$, ** $p<0.01$. The data are modified from Ref No.45 with permission.

apoptotic death in the hippocampus *via* the IL-1β/JNK signaling pathway, neurobehavioral changes, and changes in synaptic plasticity in rats[52]. Al also impairs hippocampal neurogenesis in infant mice as well as in adult mice[53,54].

3-3. Al neurotoxicity in humans

An association between Al poisoning and memory disorder in humans was first reported in 1921[55]. Later, Al was found to cause dialysis encephalopathy in hemodialysis patients because Al is present in dialysis solution or in pharmacological compounds as treatments for hyperphosphatemia[2]. Al induces various dialysis-related disorders, including osteomalacia (Al bone disease), microcytic anemia, and β_2-microglobulin-associated amyloidosis in dialysis patients[56]. Although the use of Al-containing agents in dialysis patients is prohibited in many countries, recent studies suggest an association between the serum Al level and the risk of uremic pruritus and increased mortality in chronic hemodialysis patients[57,58].

In 1988, in Camelford (Cornwall, U.K.), drinking water was accidentally contaminated by Al, and more than 20,000 people were exposed to high levels of Al for several days. Residents who were exposed to Al exhibited various symptoms related to cerebral impairment such as inability to concentrate, short-term memory loss, and poor psychomotor performance in a 10-year follow-up study[59]. Exley and Esiri demonstrated the deposition of high amounts of Al in the brain of a resident who was exposed to Al and died 15 years later[60]. This 58-year-old woman exhibited unspecified neurological symptoms and a rare form of sporadic cerebral amyloid angiopathy that was characterized by AβP deposition in blood vessels. Al-specific fluorescence microscopy along with congo red staining exhibited co-localization of Al and AβP in the brain of this patient[61]. Another case study of a resident who died 26 years after the incident exhibited similar characteristics to AD patients such as deposition of AβP and phosphorylated tau as well as increased Al in senile plaques[62]. An increased Al level was also observed in the hippocampus of another resident who suffered from epilepsy[63]. Mold *et al.* observed the intracellular accumulation of Al in inflammatory cells and glial cells in the brain of the other resident who suffered cerebral amyloid angiopathy [64]. These studies indicate that short-term exposure to Al can cause prolonged accumulation of Al in the human brain for many years and may finally cause various neurological symptoms.

4. Link between Al and Alzheimer's disease

4-1. Al and the amyloid cascade hypothesis in AD

The link between Al and AD is supported on many findings, beginning in 1965 with the finding of Klatzo *et al.* that the intracerebral administration of Al to rabbits induced the neurofibrillary degeneration and the appearance of tangle-like structures that were similar to the NFTs found in the brains of AD patients[10]. Moreover, Crapper *et al.* reported an increased level of Al in the brains of AD patients[65]. In the 1970s, Al was found to cause dementia in dialysis patients (dialysis encephalopathy) as mentioned above[2].

Although the precise causes of AD are still under investigation, numerous biochemical, toxicological, cell biological, and genetic studies have supported the "amyloid cascade hypothesis", namely, that the accumulation of AβP and its neurotoxicity play a central role in the pathogenesis of AD[66,67]. AβP is a small peptide consisting of 39–43 amino acid residues that is secreted after cleavage of the amyloid precursor protein (APP) N-terminus by β-APP cleaving enzyme (BACE) and intramembrane cleavage of its C-terminus by γ-secretase[7].

It is widely accepted that conformational changes of AβP induced by oligomerization enhance its neurotoxicity. Approaches using size-exclusion chromatography, gel electrophoresis, and atomic force microscopy have demonstrated that the soluble oligomers of AβP are synaptotoxic and neurotoxic[66].

Considering that AβP is secreted in the cerebrospinal fluid of young individuals as well as in older adults and in AD patients[68], factors that accelerate or inhibit its oligomerization may play essential roles in the pathogenesis of AD. Several factors such as peptide concentration, pH and composition of solvents, and temperature can influence the oligomerization process[67]. Interestingly, rodent (rats or mice) AβP exhibits less of a tendency to oligomerize than primate (humans or monkeys) AβP *in vitro*, and accumulation of AβP is rarely observed in the brains of rodents compared with primates[69]. The amino acid sequences of human and rodent AβP are similar; rodent AβP differs from primate AβP by only three amino acids (Arg^{5}, Tyr^{10}, and His^{13}) as shown in **Fig.3**. Considering that these three amino acids have the ability to bind metals, trace elements including Al^{3+} are of particular interest as potential acceleratory factors and might play important roles in the accumulation of AβP in the human brain.

Exley *et al.* firstly demonstrated by circular dichroism spectroscopy that Al induces a conformational change in the first 40 amino acid residues of AβP (AβP(1-40))[70]. Al has also been shown to promote the oligomerization of ^{125}I-labeled AβP(1-40), and Fe and Zn have shown similar effects[71]. Using immunoblotting and high-performance liquid chromatography, we found that Al remarkably enhances the oligomerization of AβP(1-40) compared with other metals, including Zn^{2+}, Fe^{3+}, copper (Cu^{2+}), and cadmium (Cd^{2+})[72,73]. Al-oligomerized AβP(1-40) was sodium dodecyl sulfate-stable, but it could be re-dissolved by adding deferoxamine, an Al chelator.

Other metal ions such as Zn^{2+}, Cu^{2+}, and manganese (Mn^{2+}) induced oligomerization of AβP[74-76]. However, the characteristics (size, morphology) of AβP oligomers formed in the presence of Al, Zn Cu, and Fe were different according to atomic force microscopy images[77]. Sharma *et al.* reported that Zn-oligomerized AβPs were less toxic than Cu-oligomerized AβPs[78]. For the comparison of the toxic effects of Al-oligomerized AβPs to that of Zn- oligomerized AβPs, we exposed Al-oligomerized and Zn- oligomerized AβPs to cultured hippocampal neurons[33]. After 4 days, Al-oligomerized AβPs bound tightly to the surface of cultured neurons and formed fibrillar deposits, meanwhile Zn-oligomerized AβPs were rarely observed. These results suggest that Al-oligomerized AβPs have a strong affinity for membrane surfaces of neurons and undergo minimal degradation by proteases. Indeed, Al has been shown to inhibit the degradation of AβP as a result of conformational changes. Meanwhile, AβP coupled with Al is more toxic than AβP alone, causing membrane disruption and perturbation of neural Ca^{2+} homeostasis and mitochondrial respiration[79]. Bolognin *et al.* demonstrated that Al-oligomerized AβPs induced overproduction of APP and tau, but AβP oligomers that were formed in the presence of other metals (Cu, Fe, and Zn) did not[80].

Increasing evidence suggests that chronic application of Al resulted in accumulation of AβP in cultured neurons from the rat cerebral cortex, neuroblastoma cells, and other neuronal cells[81-84]. Pratico *et al.* found that orally administered Al caused a marked increase in the amount of AβP in both its secreted and accumulated forms and increased deposition of senile plaques in AD model mice transfected with the human APP gene (Tg2576)[85]. These results are consistent with other studies demonstrating that oral Al intake induces AβP accumulation in the brain and impairs spatial learning and memory in AD model mice[86].

Furthermore, other recent studies have demonstrated the accumulation of AβP in brains of Al-intoxicated rats[87-89]. Al also induced other characteristics of AD pathogenesis such as neuronal death, synaptical changes, and memory disorders[90-93].

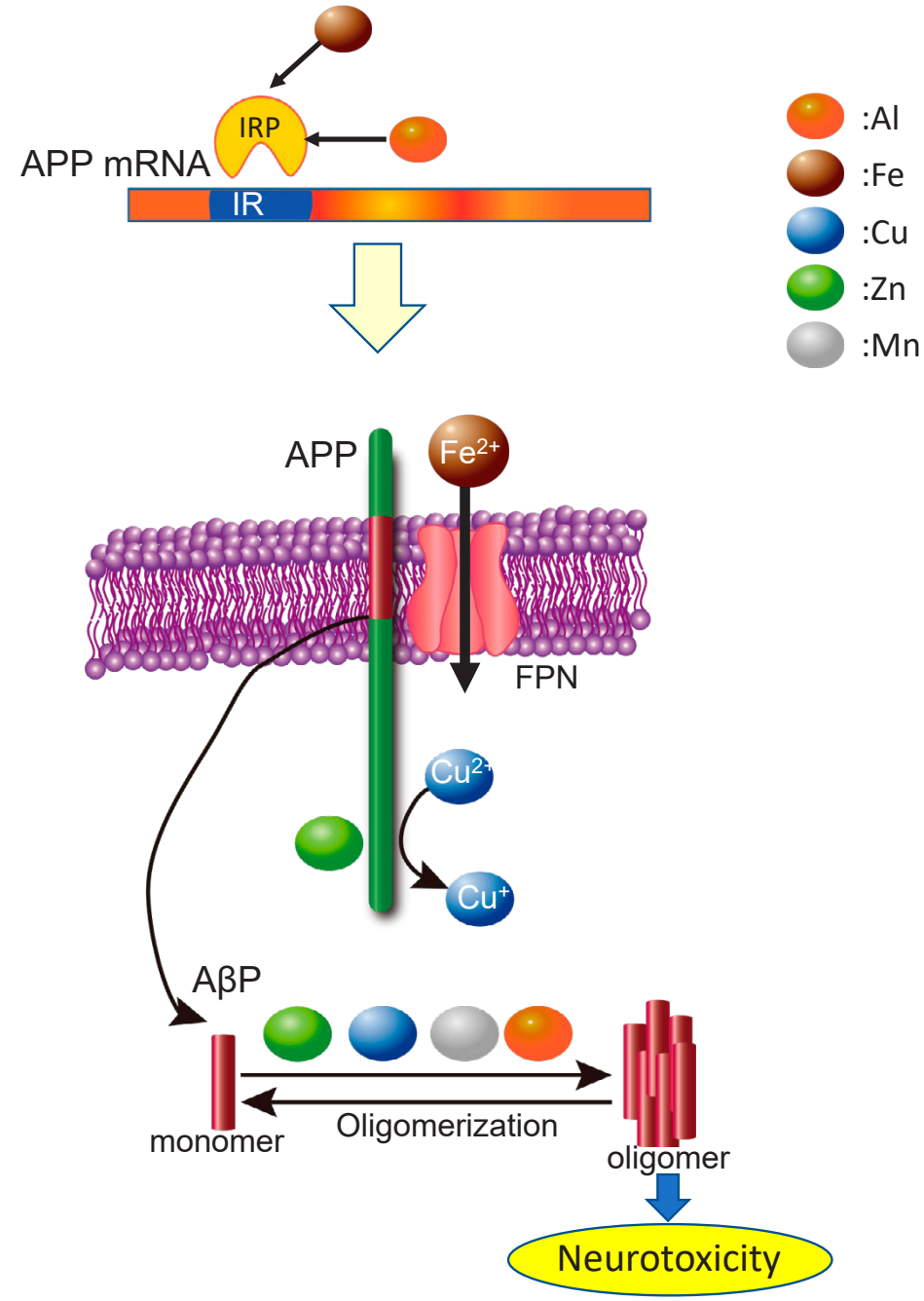

Fig. 3. **Effects of aluminum (Al) on the expression of amyloid precursor protein (APP) and the oligomerization of β-amyloid protein (AβP)**
Al can implicate in the expression of APP, the production of AβP, the neurotoxicity of AβP, and contributes to the pathogenesis of AD.
FPN :ferroportin, colored circles represent metals.

Therefore, Al-induced animal model has been used as a model for AD, and several substances were reportedly effective in the prevention of Al-induced neurotoxicity[94,95].

Al has been reported to bind and cause conformational changes in other AD-related proteins, including APP[96], tau protein, and paired helical filament-tau protein[97], and in proteins related to other diseases such as α-synuclein (*PDD and dementia with Lewy bodies (DLB)*)[98-100], islet amyloid peptide (IAPP) (*diabetes mellitus*)[101,102], ABri (*familial British dementia*)[103], ataxin 3 (*spinocerebellar ataxia type 3*)[104], and β_2-microglobulin (*dialysis-related arthropathy*)[105]. As shown in **Table 1**, Al also binds to neurofilament or to albumin and other serum proteins such as trypsin, transferrin, lactoglobulin[106]. Recent lines of evidence suggest that diverse human disorders including several neurodegenerative diseases may arise from the misfolding and aggregation of underlying proteins[107].

This concept of "conformational disease (protein misfolding diseases)" may explain the common mechanism that underlies various disorders. Under this concept, AD, prion diseases, and dementia with Lewy bodies (PDD) are categorized as conformational diseases. Considering that proteins including AβP, α-synuclein, and human IAPP are also related to conformational diseases, Al-induced conformational changes of these proteins might be associated with other neurodegenerative diseases.

Table 1. | Al-induced conformational changes of proteins

Disease-related proteins
Alzheimer's disease
AβP[1-40]: *DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV*
AβP[1-42]: *DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA*
AβP[25-35]:*GSNKGAIIGLMV*
AβP[1-16]: *DAEFRHDSGYEVHHQK*
APP
Tau or hyperphosphorylated tau (PHF-tau)
Parkinson's disease and other diseases with Lewy body
α-synuclein (NACP)
Type 2 diabetes mellitus
Islet amyloid protein (Human amylin):
KCNTATCATQRLANFLVHSSNNFGAILSSTNVGSNTY
Pro islet amyloid polypeptide (Pro IAPP)
Familial British dementia
ABri: *ASNCPAIRHPGNKPAVGTLICSRTVKKNIIGGN*
Spinocerebellar ataxia
Ataxin 3
Dialysis-related arthropathy
β_2-microglobulin
Non-disease related proteins
neurofilament
human serum albumin (HSA)
bovine serum albumin (BSA)
milk β-lactoglobulin (β-LG)
Hen Egg-white lysozyme
trypsin and trypsin inhibitor
transferrin

Al also influences the production of AβP *via* the expressions of APP and disrupts Fe homeostasis. APP is a metal-binding protein and is involved in the regulation of metal homeostasis at synapses[108]. APP possesses Cu and/or Zn binding sites at its N-terminus. APP has also been implicated in Fe^{2+} efflux along with ferroportin. Moreover, Fe controls APP expression because its mRNA possesses an IRE domain. The concentration of free Fe^{2+}, which causes formation of toxic free radicals, is generally regulated by the expression of Fe-binding proteins such as ferritin or transferrin through the IRE/iron regulatory protein (IRP) network[109]. Under Fe-deficient conditions, IRP binds to the IRE. As the concentration of free Fe^{2+} increases, the binding of Fe to IRP causes down-regulation of transferrin and up-regulation of ferritin, and the amount of free Fe^{2+} is thereby decreased. Rogers *et al.* found that APP mRNA contains an IRE domain, and their expression is regulated by Fe[110]. Other disease-related genes such as α-synuclein and prion protein also possess an IRE domain[111]. Because Al and Fe share similar chemical characteristics, Al^{3+} reportedly binds to IRP[112,113], and therefore, Al can influence the expression of Fe-binding proteins with IREs in their mRNA, resulting in elevation of the Fe concentration. Al also influences Fe uptake in cultured neurons and glial cells[114]. Indeed, Al reportedly induces elevated APP expression in experimental animals[115,116]. There have been other studies which suggested that Fe homeostasis is implicated in AD pathogenesis. A Fe-related gene, transferrin C2, was revealed to be a risk factor for AD[117], and Imagawa *et al.* reported that Fe supplementation was effective for recovery of cognitive function of familiar AD[118]. Thus, the interactions between Al and Fe may be central to the pathogenesis of AD. **Figure 3** also exhibits the effects of Al on the expression of APP, the secretion of AβP, and its oligomerization. APP is a Zn and/or Cu-binding protein and is implicating in the regulation of metal homeostasis such as controlling Fe^{2+} efflux with ferroportin (FPN) at synapse. Abnormal APP expression induced by Al leads to the disruption of metal homeostasis and the increased amount of AβP. Normally, secreted AβP is degraded by various proteases. However, AβP that is aggregated in the presence of trace metals, including Al, Zn, Cu, and Mn, is resistant to proteases and accumulates in the brain. The oligomerized AβPs can be easily incorporated into membranes and cause neuronal death. Al and other metals may participate in these degenerative processes and could be linked to the pathogenesis of Alzheimer's disease.

4-2. Accumulation of Al in the AD brain

The accumulation of Al in the brain of AD patients supports the association about Al and AD pathogenesis. After the finding of Crapper *et al.*[65], similar results supporting elevated Al in AD brains were reported[119-122], as well as the controversy results[123]. However, prior studies examining Al have been controversial because Al contamination of tissue samples can easily occur during fixation and staining. Thus, quantitative analysis of non-fixed and freshly frozen tissues is necessary. Andrási et al. reported higher Al and lower Mg and P in AD brain[124]. Although several studies have claimed that Al is absent in senile plaques or NFTs[125], this may be caused by limitations of their analytical methods in detecting low levels of Al. Bouras *et al.* used highly sensitive laser microprobe mass analysis (LAMMA) with non-fixed brain samples and reported accumulation of Al in NFT-bearing neurons of AD brains[126]. Accumulation of Al in both senile plaques and NFTs has been reported in renal failure patients[127]. Yumoto *et al.* analyzed Al using energy-dispersive X-ray spectroscopy combined with transmission electron microscopy (TEM-EDX), a method that yields a high resolution and has a low detection limit[128]. Their detailed analysis demonstrated that Al was present in cores of senile plaques at a concentrations of 35–50 ppm. They also demonstrated the co-localization of Al and Fe in the nucleus of AD brains[129]. Exley and coworkers demonstrated Al deposition colocalized with amyloid plaques and NFTs in the brains of familial AD patients using Al-specific fluorescence microscopy[130,131]. They also investigated the amount of Al in the brains of patients with various neurodegenerative diseases and found elevated Al levels in patients with sporadic AD, familial AD, ASD, and multiple sclerosis compared with controls[132]. Lukiw *et al.* reported the increased Al content in brains of AD patients by 36-year multicenter study[133]. Recent meta-analysis of 34 studies demonstrated the significantly higher Al in brain, serum, and cerebrospinal fluid of AD patients[134].

4-3. Epidemiology of Al and dementia

The reported risk factors of AD include age, gender, family history, apolipoprotein E polymorphism, head trauma, and Al. Among them, Al in drinking water has been a focus of study since 1989 when Martyn *et al.* reported a high incidence of AD in areas with high levels of Al in the drinking water in England and Wales[135]. After this initial report, a considerable number of studies provided evidence to support an association between AD and Al in drinking water[136]. McLachlan *et al.* found that an elevated risk of histopathologically verified AD is associated with the consumption of high concentrations of Al in drinking water[137]. Rondeau *et al.* demonstrated that high daily intake of Al was correlated with an increased risk of dementia or cognitive

decline in a 15-year-follow-up French cohort study[138]. A meta-analysis of eight cohort and case-control studies with a total of 10,567 individuals suggests that the chronic exposure to Al has an association with increased risk of AD[139]. Bagepally *et al.* conducted a meta-analysis of 16 studies investigating the relationship of Al with dementia that included one high quality study and 13 moderate quality studies with almost 22,000 participants[140]. Among them, one high quality study and six moderate quality studies found an association between increased Al levels in drinking water and increased dementia risk. A recent study using the Canadian Study of Health and Aging cohort data suggested an increased, although not significant, association of Al in drinking water with AD risk [141].

Considering that the amount of Al consumed in drinking water is approximately 5% of the total daily intake, it is possible that some factors that prevent or accelerate Al absorption may be present in drinking water. Silicate (Si) in water was reported to interact with Al and prevent Al toxicity in fishes. In a French cohort study, the relationship between Al and cognitive impairment was suggested to be influenced by the Si concentration[142]. Cognitive impairment among women was correlated with low Si concentrations in drinking water[143]. Meanwhile, fluoride (F) binds to Al, and aluminum fluoride (AlF_3) possesses various biological functions. Al and F in drinking water have been demonstrated to be risk factors for dementia in both men and women in Scotland[144].

Several studies have indicated that occupational exposure to Al induces adverse effects on human memory. The longitudinal study suggests a chronic Al exposure among Al workers in China can damage cognitive functions including episodic memory and that higher plasma Al level is associated with the mild cognitive impairments[145]. Shang *et al.* demonstrated by their cross-sectional study that increased Al and lithium (Li) and decreased Zn levels in plasma are related to cognitive impairment in Al workers[146]. Furthermore, plasma Al levels were associated with cognitive performance in Al-exposed workers in China[147]. Mohammed *et al.* demonstrated an association of plasma Al and tau levels and cognitive dysfunction in Al foundry workers[148]. Miners that inhaled Al dust exhibited increased mortality from AD, although the increase was not statistically significant[149]. A 55-year-old woman who was exposed to Al-containing paints and had a high serum Al level exhibited movement disorders (tremors of the hands and head, polyminimyoclonus, and dystonic posturing of the hands) and symptoms of dementia[150].

Considering these increasing new lines of evidence regarding Al, it is difficult to agree with the early criticisms of the aluminum hypothesis. Although the precise mechanism underlying AD pathogenesis remains elusive, the significance of Al in the pathogenesis of AD needs to be revisited.

5. Al and human health

5-1. Intake, bioavailability, and excretion of Al

Neurotoxicological, analytical, and epidemiological studies have demonstrated that Al is toxic to the central nervous system and causes dementia when it enters the brain, even though the link between Al and AD is controversial. Therefore, the Al levels in the body and brain are crucial to consider when determining the risk of Al to human health. The primary source of Al in humans is food. In general, the Al levels in most foods are low and vary within a wide range, although the concentration of Al in several plants are very high. The daily intake of Al is estimated to be 10-20 mg/day[151]. Contamination from food additives such as baking powder or from cooking utensils accounts for a considerable part of Al intake. The National Food Administration in Sweden reported in 1992 that the daily intake of Al in Sweden was estimated to be 13 mg[152]. Since baking powder contains Al, cakes or breads used baking powder contribute much in Al intake. The use of Al utensils was estimated to increase the Al intake by approximately 2 mg/day. As other sources of Al, Al is present in the drinking water because it is used as a coagulant in the water treatment process. Respiratory absorption of Al is important, although it is difficult to estimate. Atmospheric fine particulate matter (PM2.5) contains much Al, and rats exposed to PM2.5 dust reportedly exhibited an elevated Al level in the cerebral cortex[153].

In 1989, a joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) recommended a provisional tolerable weekly intake (PTWI) of 7.0 mg/kg body weight of Al. In 2007, this was changed to 1.0 mg/kg body weight because of its potential effects on the reproductive system and the developing nervous system. However, it was estimated that several foods contained much amount of Al and exceeded this PTWI value when the food consumed by a 16-kg infant. In 2011, this PTWI value was further changed to 2.0 mg/kg body weight[154].

5-2. The bioavailability and biological fate of Al

The absorption rate of metals including Al by the gastrointestinal tract is low and widely varies. Thus, the bioavailability of Al, namely, the amount of Al that is absorbed in the gastrointestinal tract and transported to the brain through the blood brain barrier, is crucial for human health. The lack of appropriate radioactive isotopes of Al has made it difficult to study on Al bioavailability. However, the analyses using accelerator mass spectrometry and ^{26}Al, a non-radioactive isotope of Al, have advanced this area of study[155]. Using this approach, it became clear that a small amount of Al (approximately less than 1%) is absorbed from food *via* the gastrointestinal pathway; however, this amount is influenced by various factors including individual differences, age, pH, stomach contents, chemical speciation of Al, and coexisting substances[156]. For example, the absorption of Al hydroxide ($Al(OH)_3$), a main component of antacids, is much lower than that of Al citrate. The coexistence of organic ligands such as citric acid or maltol promotes the absorption of Al, while Si prevents its absorption. Although the consumption of tea greatly contributes to the daily intake of Al, the Al in tea infusion is adsorbed at a low level[157]. It is possible that Al eluted from cooking utensils is highly bioavailable because the stopping of the use of Al utensils has decreased serum Al levels[158]. Fe, which possesses similar chemical characteristics to Al, in the utensils is reportedly also easily adsorbed[159,160]. Arabi *et al.* demonstrated that mice exposed to boiled water from old Al cookware exhibited cytotoxic and genotoxic changes[161]. The rate of Al absorption is increased in older people, patients with Down's syndrome, and patients with AD[162].

Once absorbed from the gastrointestinal tract, Al rapidly appears in the blood, and approximately 80% of Al is transported by binding to transferrin, a Fe transporter protein; the remaining Al binds to albumin and citrate[163]. Approximately 50% of Al in the serum is excreted in the urine through the kidneys. Thus, high Al levels are observed in the bodies of patients with renal failure or kidney disease. Additionally, half of the Al amount is accumulated in the bone. A small, but considerable amount of Al can cross the blood brain barrier, possibly through the transferrin-receptor pathway or monocarboxylate transporters, and enter the brain. Then, Al remains in the brain and accumulates semi-permanently[136,164]. Kobayashi *et al.* reported that intraperitoneally or orally administered ^{26}Al was transferred to the brain and the amount of Al in the brain was not changed after 35 days, although Al in the serum disappeared rapidly[165]. The amount of Al in human bodies increases in age-dependent manner, although other trace elements don't[166]. Thus, it is possible that the brain has little ability to eliminate Al. **Figure 4** summarizes the biological fate of Al from various sources.

5-3. Iatrogenic exposure to Al

The Al present in medications has a crucial effect on human health because of its high bioavailability. A considerable amount of contamination is present in total parenteral nutrition (TPN). Al in TPN solutions is completely absorbed and enters the blood. Although a part of Al in the blood is excreted from the kidneys, some patients receiving TPN solutions have renal failure. In particular, the renal functions of infants have not been fully developed, and infants are considered to be more susceptible to Al in TPN. The accumulation of Al in bones of patients receiving TPN has been reported. Bishop *et al.* reported that preterm infants who received TPN containing high concentrations of Al had lower mental development scores than age-matched infants who received TPN with low Al levels[167]. Based on these findings, The U.S. Food and Drug Administration (FDA), North American Society for Pediatric Gastroenterology and Nutrition, and other societies have recommended reduction of Al contamination in TPN solutions. The FDA published a final rule requiring the concentration of Al in TPN solutions to be labeled by 2000, and the rule has been in effect from 2003[168]. In Japan, the method for determination of Al in TPN solutions was added to the Japanese Pharmacopoeia in 2006.

Another source of Al for infants is milk and formula[169]. High levels of Al are found in infant formulas. Yumoto *et al.* demonstrated that ^{26}Al administered to mother rats was transported to the brain of suckling infants through maternal milk suggesting that it would happen in humans [170]. In fact, Ma *et al.* reported that higher concentrations of Al in nails of infants were associated with low fine motor score[171].

A large amount of Al is present in antacids, and therefore, continuous exposure of patients with renal failure or kidney diseases to Al-containing antacids may increase their risk of encephalopathy. In 2002, the Japanese Ministry of Health, Labour and Welfare recommended that patients on dialysis or with renal failure should not use Al-containing antacids.

Al compounds, such as $Al(OH)_3$ or Al phosphate, are widely used as adjuvants in various vaccines. Using the ^{26}Al technique, Al in vaccines was shown to be absorbed and appeared in serum and other tissues of rats after intramuscular injection[172]. Weisser investigated the increase in serum Al levels and accumulation of Al in the bones of rats after intramuscular injection of

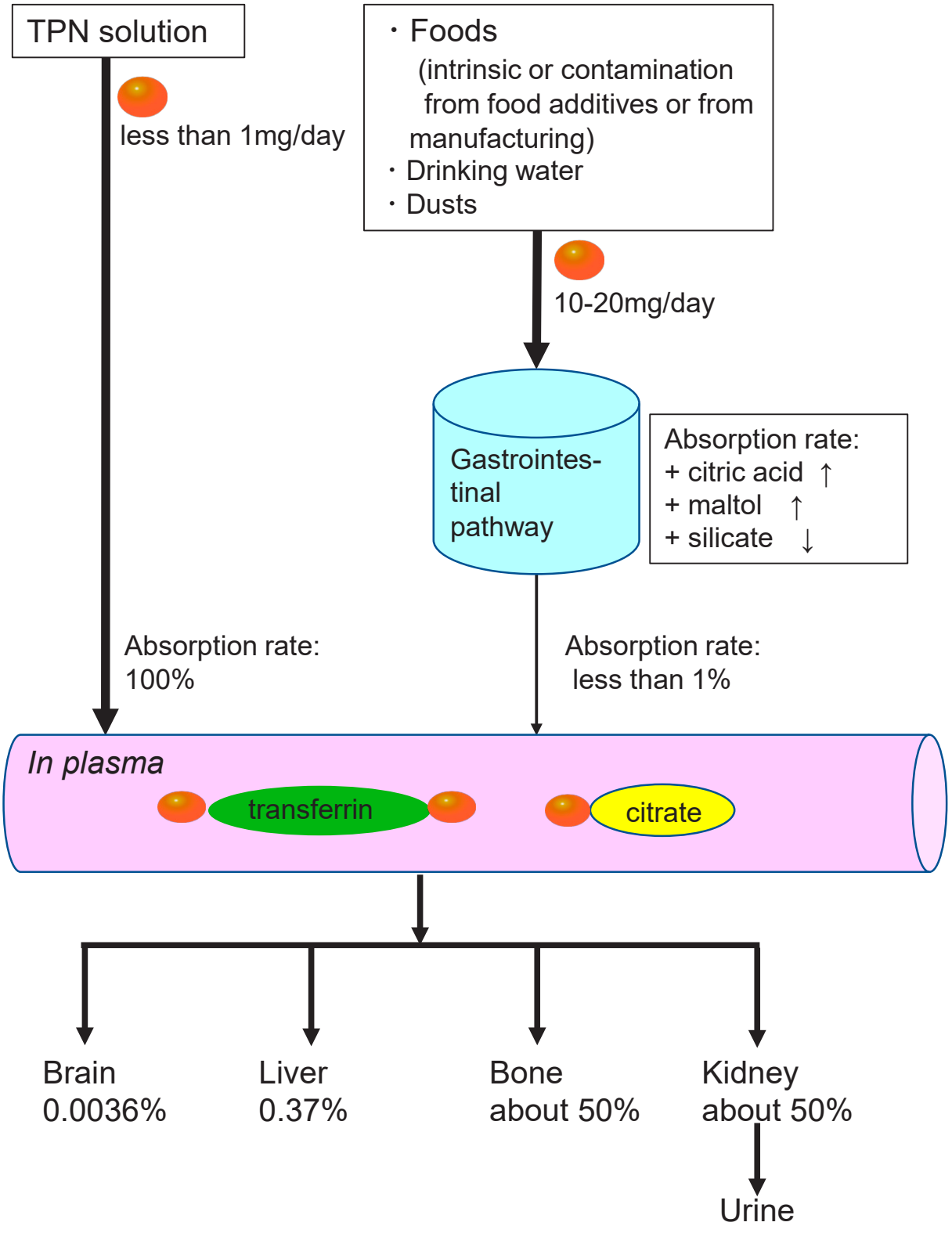

Fig. 4. **Intake and bioavailability of aluminum (Al)**
The daily intake of Al is estimated to be 10–20 mg from intrinsic foods and contamination by food additives or utensils. In general, the gastrointestinal absorption rate is less than 1%. However, this rate varies in individuals and is largely influenced by age, pH, stomach contents, chemical speciation of Al, and coexistence of substances such as silicic acid. Once Al enters the blood flow, a small but considerable amount of Al passes through the blood brain barrier, enters the brain, and accumulates throughout the lifetime. The absorption rates were obtained from Ref. No. 163.

vaccines with Al adjuvants[173]. An association between Al-containing vaccines and Gulf War Syndrome and other diseases has been suspected[174]. Gulf War Syndrome is a multi-system disorder afflicting many veterans of the 1990–1991 Gulf War.

Petrik *et al.* demonstrated that subcutaneous injection of $Al(OH)_3$ caused apoptotic death of motor neurons and impaired motor functions of mice in addition to producing Al deposition in motor neurons[175]. Furthermore, the link between Al adjuvants and autism spectrum disorders (ASD) has been discussed for many years[176]. High Al concentrations are observed in the brains of ASD patients[132]. Considering that infants receive much more Al from vaccines than other sources, the risk of Al-containing vaccines should be revisited.

6. Conclusion

Al is widely accepted as a neurotoxin and can cause cognitive deficiency and dementia when it enters the brain. Growing analytical, toxicological, and epidemiological studies support a link between Al and AD. Moreover, Al can affect infants, older adults, and patients with impaired renal functions and can cause severe health problems in these populations. Because Al is not excreted from the brain and accumulates for the long-term, unnecessary exposure to Al should be avoided. The link between Al and neurodegenerative diseases may provide a seed for the treatments/prevention of the diseases. The characteristics of Al neurotoxicity are complex, and further detailed research is necessary, particularly in relation to its bioavailability, cellular effects, metabolism, and metal-metal interactions.

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