SAGE-Hindawi Access to Research
International Journal of Alzheimer's Disease
Volume 2011, Article ID 276393, 17 pages
doi:10.4061/2011/276393

Review Article

Link between Aluminum and the Pathogenesis of Alzheimer's Disease: The Integration of the Aluminum and Amyloid Cascade Hypotheses

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Received 15 September 2010; Revised 29 November 2010; Accepted 5 January 2011

Academic Editor: Paolo Zatta

Whilst being environmentally abundant, aluminum is not essential for life. On the contrary, aluminum is a widely recognized neurotoxin that inhibits more than 200 biologically important functions and causes various adverse effects in plants, animals, and humans. The relationship between aluminum exposure and neurodegenerative diseases, including dialysis encephalopathy, amyotrophic lateral sclerosis and Parkinsonism dementia in the Kii Peninsula and Guam, and Alzheimer's disease (AD) has been suggested. In particular, the link between aluminum and Alzheimer's disease has been the subject of scientific debate for several decades. However, the complex characteristics of aluminum bioavailability make it difficult to evaluate its toxicity and therefore, the relationship remains to be established. Mounting evidence has suggested that significance of oligomerization of β-amyloid protein and neurotoxicity in the molecular mechanism of AD pathogenesis. Aluminum may play crucial roles as a cross-linker in β-amyloid oligomerization. Here, we review the detailed characteristics of aluminum neurotoxicity based on our own studies and the recent literatures. Our aim is to revisit the link between aluminum and AD and to integrate aluminum and amyloid cascade hypotheses in the context of β-amyloid oligomerization and the interactions with other metals.

1. Introduction

Aluminum (Al) is abundantly distributed in our environment, and compounds containing Al have been used in manufacturing (e.g., clays, glasses, and alum) for centuries. Despite its abundance, Al was first isolated as an element in 1827, and its use as being a silvery metal began only after 1886. Al is a new metal in this context. Because of its beneficial characteristics such as a lightweight, nonmagnetic, malleable, and ductile element, Al has a widespread and important use in industrial applications and consumer products. Al is also used in cooking utensils and in pharmacological agents including antacids and antiperspirants from which the element enters the human body.

Al is not essential for life. On the contrary, Al is a well established neurotoxin and is suspected to be linked with various neurodegenerative diseases including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Parkinsonism dementia in the Kii Peninsula and Guam [1], and the Gulf War syndrome [2].

In particular, a possible relationship between Al and the pathogenesis of AD has been discussed for several decades [3–7]. AD is a severe senile type of dementia first reported in 1906. The pathological hallmarks of AD are the deposition of extracellular senile plaques, intracellular neurofibrillary tangles (NFTs), and the selective loss of synapses and neurons in the hippocampal and cerebral cortical regions. The major component of NFTs is the phosphorylated tau protein. Senile plaques are largely comprised of β-amyloid protein (AβP) [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 [9–11]. In spite of these findings, the aluminum hypothesis has been the subject of much debate and criticism for several decades. During this period, great progress was made in AD research. Particularly, numerous studies have supported the idea termed "amyloid cascade hypothesis", namely that the conformational changes of AβP and its neurotoxicity play a central role in AD pathogenesis [12, 13]. Al^{3+} and other metals including Zn^{2+}, Cu^{2+}, and Fe^{3+} influence the oligomerization and conformational changes of AβP as cross-linkers, and, therefore, their implications are important in this context. Furthermore, increasing evidence suggests the implication of these metals in the pathogenesis of AD [14–16]. Al binds to various metal-binding proteins and influences homeostasis of other metals.

We review here the detailed characteristics of aluminum neurotoxicity based on our own studies and the recent literature. Our aim is to update the various adverse effects of Al and revisit the link between Al and AD based on new findings on Al-induced conformational changes and metal-metal interactions.

2. Neurotoxicity of Aluminum Update

2.1. Effects of Al on the Memory Disorder of Human: Historical Overview. An association between Al poisoning and memory disorder in humans was first reported in 1921 [17]. Later, it was shown that the intracerebral administration of Al induced epilepsy in experimental animals [18]. As a component of dialysis solutions or Al-containing pharmacological compounds, Al is known to cause various dialysis-related disorders, including osteomalacia (aluminum bone disease), microcytic anemia, β_2-microglobulin-associated amyloidosis [19], and dialysis encephalopathy in hemodialysis patients [20].

The accidental contamination of Al into drinking water occurred and more than 20,000 persons were exposed to high level of Al at 1988 in Camelford (Cornwall, UK). Residents exposed to contaminated Al exhibited various symptoms related to cerebral impairments such as loss of concentration and short term memory in a 10-year follow-up study [21].

Martyn et al. reported a high incidence of AD in areas with a high level of Al in the drinking water in England and Wales [11]. A considerable number of studies have provided evidence to support an association between AD and Al in drinking water after this initial report [22]. Frecker reported on a Norwegian area where high Al concentrations in drinking water were linked with high dementia mortality [23]. Neri and Hewitt found a positive relationship between Al in drinking water and AD risk in Canada [24]. Forbes and McLachlan demonstrated a greater risk of AD in Canadian areas where concentrations of Al are high and those of fluoride are low [25]. Rondeau et al. demonstrated that high daily intake of Al was correlated with increased risk of dementia or cognitive decline in a 15-year follow-up French cohort study [26–28]. These studies suggest that Al has adverse effects on human memories and causes dementia when it enters the brain.

2.2. Effects of Al on the Central Nervous System In Vitro or In Vivo. Despite it's environmental abundance, Al is not an essential element for living organisms, and no enzymatic reaction requires Al. Al is reported to influence more than 200 biologically important reactions and to cause various adverse effects on the mammalian central nervous system (CNS) (Table 1). These include crucial reactions for brain development such as the axonal transport, neurotransmitter synthesis, synaptic transmission, phosphorylation or dephosphorylation of proteins, protein degradation, gene expression, and inflammatory responses.

Al exhibits only one oxidation state, Al^{3+}. Al^{3+} has affinity for negatively charged, oxygen-donor ligands. Inorganic and organic phosphates, carboxylate, and deprotonated hydroxyl groups form strong bonds with Al^{3+}. Owing to these chemical characteristics, Al^{3+} binds to the phosphate groups of DNA and RNA, affecting DNA topology and influencing the expression of various genes essential for brain functions. Lukiw et al. reported that nanomolar levels of Al^{3+} were sufficient to influence neuronal gene expression [33, 35].

Al^{3+} also binds to the phosphate groups of nucleoside di- and triphosphates, such as ATP and can thus influence energy metabolism. Furthermore, Al inhibits the functions of various protein kinases and phosphatases.

Al^{3+} has very low ligand-exchange rate in comparison to other metals. 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. 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+}. These properties make Al useless in enzymatic reactions and increase its half-life in the human body. We show the typical effects of Al in Figure 1.

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^{+} (Figure 2). Thus, 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; this property has made it useful as a leather tanning agent. 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 neurofilament and microtubule-associated proteins (MAPs), and so forth [58].

Consequently, Al causes apoptotic death of neurons and glial cells. Chronic administration of Al impairs long-term potentiation (LTP), which is a form of synaptic information storage well-known as a paradigm of memory mechanisms. Al also impairs various enzymes including those related to neurotransmitter synthesis and thus affects the neurotransmitter content. Al^{3+} also inhibits voltage-gated Ca^{2+} channels and neurotransmitter receptors, and impairs synaptic transmission. Finally, Al causes spatial memory deficit, influences emotional reactivity, and impairs various brain functions related to learning and memory.

Table 1: Effects of aluminum on the central nervous system.

	References
(1) Nucleus and gene expression	
Binding to DNA	
Binds to histone-DNA complex and induces conformational changes of chromatin.	[29]
Induces topological changes of DNA.	[30, 31]
Altered gene expression	
Induces decreased expression of neurofilament and tubulin.	[32]
Induces altered expression of genes of neurofilament, APP, and neuron specific enolase.	[33]
Induces decreased expression of transferrin receptor.	[34]
Induces altered expression of RNA polymerase I.	[35]
Induces downregulation of mitochondrial cytochrome c oxidase.	[36]
Induces altered expression of calbindin-D28k.	[37]
Induces decrease in the expression of nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF).	[38]
Induces expression of pro-inflammatory genes and pro-apoptotic genes.	[39]
Induces elevated expression of APP.	[40, 41]
Induces altered expression of oxidative stress marker genes (SOD1, glutathione reductase, etc.).	[42]
Induces decreased expression of neprilysin.	[43]
Induces altered expression of β-APP secretase (BACE1 and BACE2).	[40, 44]
(2) Cellular functions	
Energy metabolism	
Inhibits the activity of hexokinase	[45]
Inhibits the activity of phosphofructokinase	[46]
Inhibits the activity of glucose-6-phosphate dehydrogenase	[47]
Causes mitochondrial dysfunction and depletion of ATP	[48, 49]
Decreases in activity and expression of TCA-cycle related enzymes (succinate dehydrogenase (SDH), alpha-ketoglutarate dehydrogenase (KGDH), isocitrate dehydrogenase-NAD^+ (IDH), fumarase (FUM), aconitase (ACN), and cytochrome c oxidase (Cyt C Ox)).	[50]
Phosphorylation and dephosphorylation	
Inhibits the activity of protein phosphatase.	[51]
Increases the activity of protein kinase C and cytoskeleton proteins.	[52]
Accelerates phosphorylation and accumulation of neurofilament.	[53]
Enhances Ca^{2+}/Calmodulin dependent protein kinase activity.	[54]
Accelerates phosphorylation of MAP 2 and neurofilament.	[55]
Inhibits dephosphorylation of tau.	[56]
Induces nonenzymatic phosphorylation of tau.	[57]
Abnormal accumulation of proteins	
Causes the conformational change and the accumulation of neurofilament and MAP1A, MAP1B.	[58]
Accelerates the phosphorylation of tau and its accumulation.	[59]
Causes the accumulation of tau protein in neuroblastoma cells or in primary cultured neurons.	[60, 61]
Causes the accumulation of tau protein in experimental animals.	[33, 62, 63]
Causes neurofibrillary degeneration *in vivo*.	[9]
Causes the accumulation of AβP in cultured neurons or in neuroblastoma cells.	[64, 65]
Causes the accumulation of AβP *in vivo*.	[44, 66, 67]
Neurotransmitter release	
Inhibits glutamate release.	[68]
Impairs synaptic transmission.	[69, 70]
Inactivates glutamate dehydrogenase.	[71]
Inhibits NMDA-type glutamate receptor.	[72]
Inhibits choline acetyl transferase and tyrosine hydroxylase, glutamate decarboxylase.	[73, 74]

Table 1: Continued.

	References
Influences acetyl-CoA and inhibits acetylcholine release.	[75]
Activates monoamine oxidase.	[76, 77]
Inhibits dopamine beta-hydroxylase.	[78]
Inhibits uptake of serotonin and noradrenalin in synaptosomes.	[79]
Channel inhibition	
Influences the activities of Na^+ channels and K^+ channels.	[80]
Enhances the voltage-activated Na^+ channels.	[81]
Inhibits the voltage-gated calcium channel.	[70, 82]
Inhibits the IP^3-mediated Ca^{2+} release.	[83]
Others	
Influences GTP binding proteins as aluminum fluoride.	[84]
Inhibits GAP junction.	[85]
Inhibits axonal transports.	[86]
Binds to calmodulin and inhibition of calmodulin-binding enzymes.	[87]
Induces inflammatory responses.	[88]
(3) Membrane lipids	
Peroxidation	
Accelerates iron-induced membrane lipid peroxidation.	[89]
Enhances lipid peroxidation in liposomes.	[90]
Induces peroxidation of myelin lipids *in vivo*.	[91]
Increases peroxidation products (malondialdehyde).	[59]
Membrane properties	
Causes the change the lipid/phospholipids profiles of myelin *in vivo*.	[92]
Induces the change in membrane physical properties (surface potential, lipid fluidity, and lipid arrangement).	[91]
Induces the change of membrane fluidity.	[93]
(4) Higher functions	
Cell death	
Causes the apoptotic neuronal death.	[94, 95]
Causes the apoptosis of astrocytes.	[96]
Causes the death of motor neuron.	[97, 98]
Behavior, learning, and memory, others	
Inhibits long term potentiation (LTP).	[99, 100]
Causes learning disorder or memory deficit in experimental animals.	[101–103]
Influences electrical activity in hippocampus and inhibits spatial learning memory deficit in aging rats.	[104]
Causes memory deficit in AD model mice.	[105, 106]
Causes encephalopathy in dialysis patients.	[20]
Causes encephalopathy in patients with renal failure.	[107]

These adverse effects may be involved in the mechanisms that underlie Al-induced memory disorder.

3. Link between Al and AD

3.1. Historical Overview of Aluminum Hypothesis and Arguments. A link between Al and AD is supported on many fronts, beginning in 1965 with the finding of Klatzo et al. that the intracerebral administration of Al to experimental animals induced neurofibrillary degeneration and the appearance of tangle-like structures that were similar to the NFTs found in the brains of AD patients [9]. Crapper et al. reported an increased level of Al in the brains of AD patients [10]. In the 1970s, Al in dialysis solutions or pharmacological compounds was found to cause dementia in dialysis patients (dialysis encephalopathy) [20]. As noted previously, several epidemiological studies reported a high percentage of AD cases in areas with high Al level in drinking water [11, 19].

Despite supporting evidence, the aluminum hypothesis of AD remains controversial and has been the subject of much debate in the past few decades. There were at least three arguments against the aluminum hypothesis. *First*,

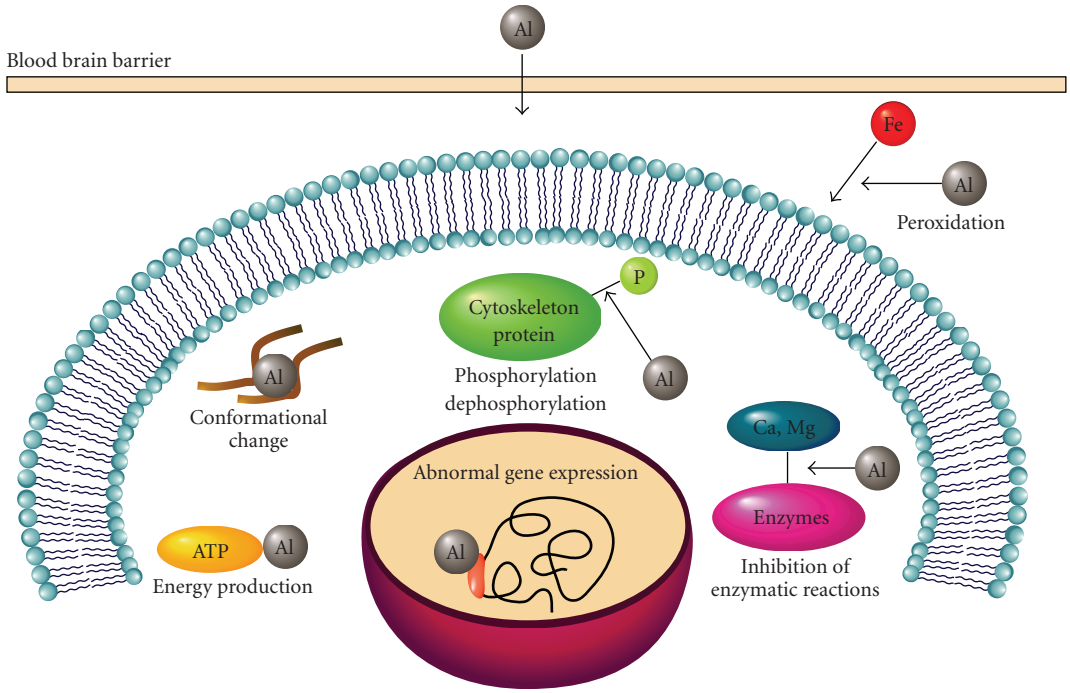

Figure 1: Effects of aluminum on the central nervous system. Major biological effects of Al on the central nervous system are depicted.

it has been argued that neurofibrillary changes in Al-intoxicated animals (Al-NFTs) are different from those in AD patients (AD-NFTs) [108]. Arguments cite morphological and biochemical differences such as the lack of paired helical filamental (PHF) structures, their different distributions in nerve terminals, and the absence of immunoreactivity for tau protein, which is the main component of NFTs in AD patients. *Second*, there is no significant difference in Al levels of AD patients and age-matched controls [109]. *Third*, the epidemiological studies on Al in drinking water are immature and inconclusive [110]. However, most of these criticisms were made in the 1990s. We would like to reinvestigate these early arguments in the context of new findings in the study of AD.

Regarding the first argument, more recent immunohistochemical studies have indicated that depositions in the brains of Al-intoxicated animals are stained with the anti-tau antibody [62, 63]. The accumulation of tau protein was reported in patients with dialysis encephalopathy [111], and in Al-intoxicated cultured neuronal cells [60, 61]. Al inhibits the dephosphorylation of tau [56] and enhances its aggregation *in vitro* [112]. Furthermore, NFTs in some AD patients have been shown to be composed of straight-type filaments rather than PHF-type filaments as is observed in Al-NFT [113]. These data indicate that attempts to discredit the aluminum hypothesis on the basis of differences between Al-NFTs and AD-NFTs are no longer tenable.

3.2. Accumulation of Al in AD Brain. Another argument cites a lack of significant difference between Al levels in AD patients and age-matched controls. One reason for the controversy may be Al contamination of the solutions used in the process of tissue fixation and staining. Therefore, prior studies in fixed tissues cannot be relied upon for precise measures of Al; quantitative analysis of nonfixed and freshly frozen tissues is necessary. One such study showed that the amount of Al in whole brains of AD patients was not significantly different in comparison to controls [114]. Landsberg et al. claimed that they could not detect Al in senile plaques or NFTs using nuclear microscopy [115]. However, this failure could simply be due to low detection limits of their analytical method. Bouras et al. used highly sensitive laser microprobe mass analysis (LAMMA) with nonfixed brain samples and reported an accumulation of Al in NFT-bearing neurons of AD brains [116]. An accumulation of Al in both senile plaques and NFTs has been reported in renal failure patients [117]. Recently, Yumoto et al. analyzed Al using energy-dispersive X-ray spectroscopy combined with transmission electron microscopy (TEM-EDX), a method which yields a high-resolution and low detection limit. Their detailed analysis demonstrated that Al was present in cores of senile plaques at a concentration of 35–50 ppm [118].

3.3. Epidemiological Studies of AD and Al in Drinking Water. Some epidemiological studies have failed to demonstrate the relationship between Al and AD [119, 120]. However, there are a number of possible explanations for this inconsistency, particularly when considering the difficulty in making side-by-side comparisons of epidemiological studies of Al (e.g., intake estimations, effect of move, changes in water-treatment processes, etc.). Using strict neuropathological criteria to discriminate between AD patients and controls (including histopathological verification), McLachlan et al.

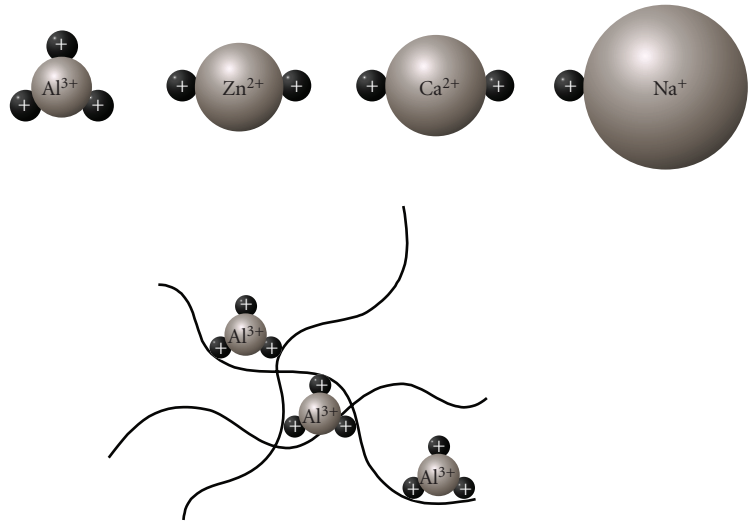

Figure 2: Cross-linking of protein by Al^{3+}. Al^{3+} has a relatively small ionic radius (50 pm) with 3 positive charges; here it is compared to other metal ions such as Zn^{2+} (74 pm), Ca^{2+} (99 pm), and Na^{+} (95 pm). These characteristics enable Al to be an effective cross-linker of proteins.

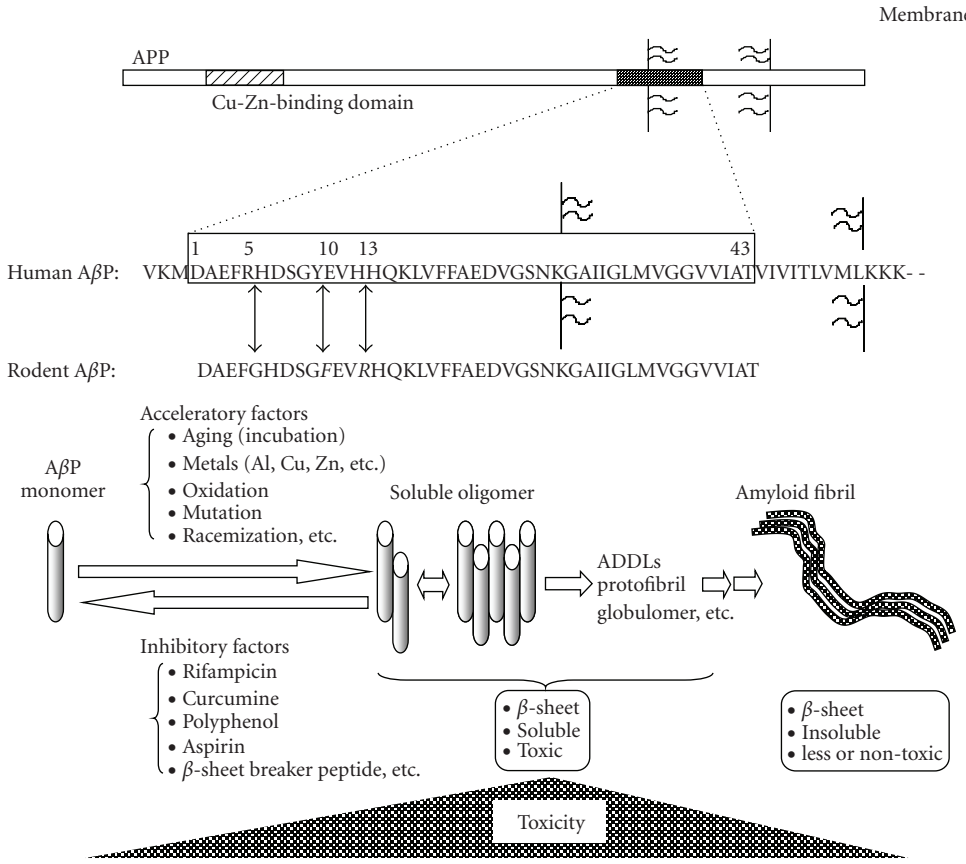

Figure 3: Secretion of AβP from APP and its oligomerization. AβP is secreted by the cleavage of the APP N-terminus by β-secretase (BACE), followed by the intramembrane cleavage of the C-terminus by γ-secretase. APP also binds to Cu or Zn. Human AβP and rodent AβP differ by 3 amino acids (Arg^5, Tyr^{10}, and His^{13}). AβP monomers form random-coil structures. However, under aging conditions or the existence of trace metals such as Al, Zn, and Cu, AβP self-aggregates and oligomerizes (dimmer to protofibrils), and then forms insoluble amyloid fibrils. Although monomeric AβPs are not toxic, oligomeric AβPs induce marked neuronal death.

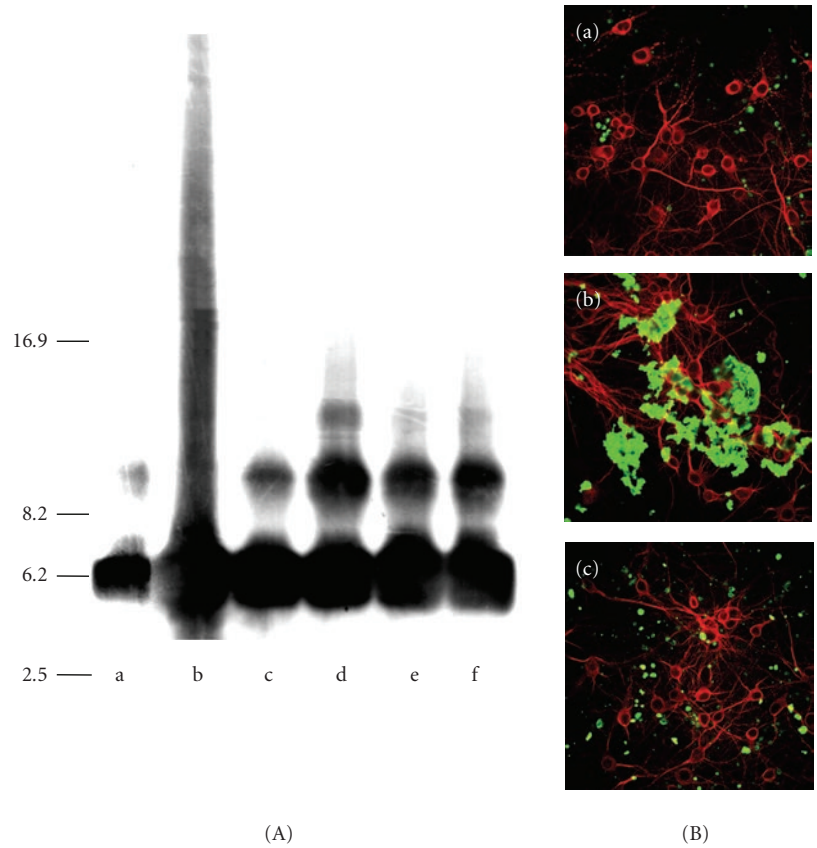

Figure 4: Aggregation of AβP by Al and other metals. (A) Immunoblotting of AβP preincubated with Al and other metals. The solutions of AβP(1–40) were incubated at 37°C for 24 h with or without 1 mM of various metals, and were analyzed by SDS-PAGE and immunoblotting using an antibody to AβP. Each lane contained 4 μg AβP(1–40). Lane a: control, b: $AlCl_3$, c: $ZnCl_2$, d: $CuCl_2$, e: $FeCl_3$, f: $CdCl_2$, Modified from [134]. (B) Deposition of AβP on surfaces of cultured neurons. Solutions of AβP(1–40) preincubated at 37°C for 24 h (a), with 1 mM $AlCl_3$ (b), or 1 mM $ZnCl_2$ (c) were applied to cultured rat cortical neurons. After 2 days of exposure, cells were washed and double immunostained with a polyclonal antibody to AβP (green) and a monoclonal antibody to MAP2 (red), and observed by laser confocal microscope. Scale bar: 50 μm, modified from [64].

found an elevated risk of histopathologically verified AD to be associated with the consumption of higher concentrations of Al in drinking water [121]. More detailed analysis revealed an association between exposure to organic monomeric Al and AD, even after adjustment for education level, family history and presence of the apoE4 allele [122].

The amount of Al consumed in drinking water is approximately 5% of the total daily intake. Thus, it is possible that some factors that prevent or accelerate Al absorption may exist in drinking water. Silicate in the water was reported to interact with Al and prevent Al toxicity to fish [123, 124]. Therefore, the level of silicate in drinking water may also be important. In a French cohort study, the relationship between Al and cognitive impairment is suggested to be influenced by the silica concentration [29]. Cognitive impairment among women was correlated with low concentrations of silica in drinking water [125].

In considering the above new lines of evidence about the neurotoxicity and epidemiology of Al, it is difficult to agree with the early criticisms of the aluminum hypothesis.

3.4. Effects of Al on the Oligomerization of AβP. In the 1990s when the early arguments were claimed, Al-induced Alzheimer-like pathological changes were first attributed to tau proteins (NFT). However, 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 [12, 13].

AβP is a small peptide of 39–43 amino acid residues, secreted by 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. Genetic studies of early-onset cases of familial AD indicated that APP mutations and AβP metabolism are associated with AD [126]. Yankner et al. reported that the first 40 amino acid residues of AβP (AβP(1–40)) caused the death of cultured rat hippocampal neurons or neurodegeneration in the brains of experimental animals [127]. AβP is a hydrophobic peptide with an intrinsic tendency to self-assemble and form SDS-stable oligomers in aqueous solution. The monomeric form

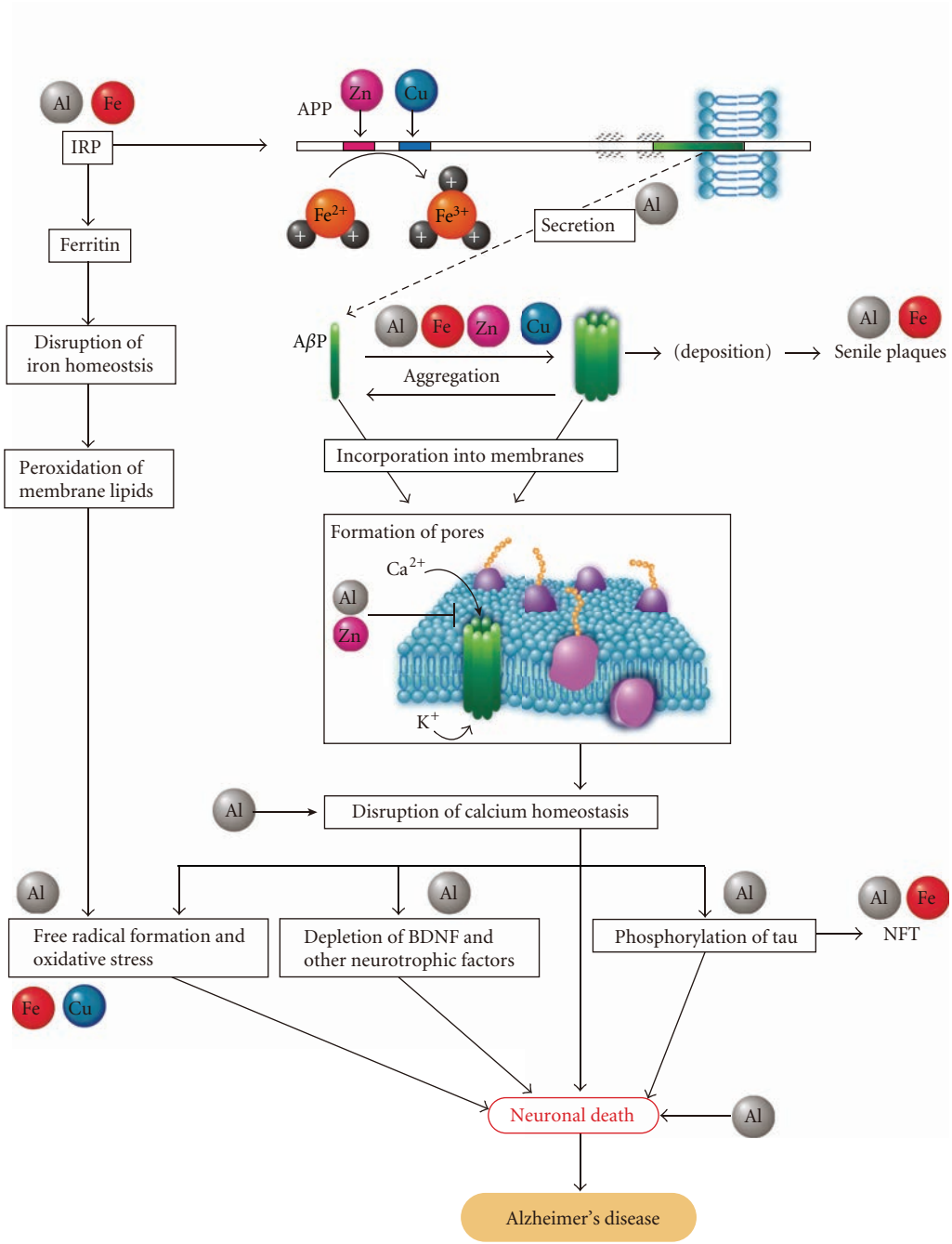

Figure 5: Modified aluminum hypothesis addressing the implications of Al and other trace metals in the pathogenesis of Alzheimer's disease. This model describes the implication of Al and other trace metals including Fe, Cu, and Zn in APP processing, generation and oligomerization of AβP, and the neurotoxic effects caused by AβP. Details are descried in the text.

of AβP has a random coiled structure. Oligomeric AβPs have β-pleated sheet structures and form insoluble aggregates, termed amyloid fibrils. Neurotoxicity of AβP(1–40) peptides was enhanced by the process of "aging" (aggregated under incubation at 37°C for several days) compared to freshly prepared AβP(1–40) in cultured neurons [128], and were correlated with its β-sheet contents [129]. Recent approaches using size-exclusion chromatography, gel electrophoresis, and atomic force microscopy have demonstrated that the soluble oligomers are synaptotoxic and neurotoxic [130]. Figure 3 exhibits the oligomerization of AβP and its neurotoxicity.

Considering that AβP is secreted in the cerebrospinal fluid (CSF) of young individuals as well as in aged or dementia patients [146], factors that accelerate or inhibit oligomerization may play essential roles in the pathogenesis

Table 2: Al-induced conformational changes of various proteins.

Proteins	References
Disease-related proteins	
Alzheimer's disease	
AβP (1-40)	[64, 131–134]
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV	
AβP (1-42):	[135, 136]
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA	
AβP (25-35):	[137]
GSNKGAIIGLMV	
APP	[138]
Tau or hyperphosphorylated tau (PHF-tau)	[32, 57, 139]
Perkinson's disease and other diseases with Lewy body	
α-synuclein (NACP)	[140, 141]
Type 2 diabetes mellitus	
Amylin:	[142]
KCNTATCATQRLANFLVHSSNNFGAILSSTNVGSNTY	
Familial British dementia	
ABri:	[143]
ASNCPAIRHPGNKPAVGTLICSRTVKKNIIGGN	
Spinocerebellar ataxia	
Ataxin 3	[144]
Dialysis-related arthropathy	
β_2-microglobulin	[145]

of AD. Several factors such as peptide concentration, pH or composition of solvents, and temperature can influence the oligomerization processes [147].

Interestingly, rodent AβP exhibits less tendency to oligomerization than human AβP *in vitro* [148] and the accumulation of AβP is rarely observed in the brains of rodents (rats or mice) as compared to primates (humans or monkeys). As shown in Figure 3, the amino acid sequences of human and rodent AβP are similar, but rodent AβP differs from primate only 3 amino acids (Arg^5, Tyr^{10}, and His^{13}) from primate AβP. All 3 amino acids have the ability to bind metals. Therefore, trace elements including Al^{3+} are of particular interest as potential acceleratory factors and may play important roles in the accumulation of AβP in the human brain.

Table 2 summarizes the effects of Al^{3+} on conformational changes of AβP and other various disease-related proteins. Exley et al. first demonstrated by CD spectroscopy that Al induces a conformational change in AβP(1–40) [131]. Al has also been shown to promote the aggregation of ^{125}I-labelled AβP(1–40), with similar findings for Fe and Zn [132]. Bush et al. demonstrated that Zn^{2+} and Cu^{2+} caused the oligomerization of AβP [149, 150]. However, role of Zn^{2+} in AD is complex and enigmatic. Lovell et al. reported that zinc has the protective effects against AβP-induced neurotoxicity [151]. We have demonstrated that Zn^{2+} blocks AβP-channels formed on membranes and inhibits the neurotoxicity [152].

We have developed a system for investigating AβP oligomerization that involves immunoblotting and precipitation. Using this system, we have demonstrated that Al enhances the polymerization of AβP(1–40) and forms SDS-stable oligomers *in vitro* [64, 133, 134]. The aggregated AβP(1–40) is redissolved by adding deferoxamine (DFO), an Al chelator. The oligomerization induced by Al is more marked than that induced by other metals, including Zn^{2+}, Fe^{3+}, Cu^{2+}, and Cd^{2+} (Figure 4(A)). Furthermore, while Al-aggregated AβPs bind tightly to the surface of cultured neurons and form fibrillar deposits, Zn-aggregated AβPs are rarely observed on the surface of cultured neurons (Figure 4(B)). These results suggest that Al-aggregated AβPs have a strong affinity for membrane surfaces as a result of minimal degradation by proteases. Indeed, Al has been shown to inhibit the degradation of AβP as the result of conformational changes [43, 153]. Furthermore, AβP coupled with Al is more toxic than normal AβP causing membrane disruption or perturbation of neural Ca^{2+} homeostasis and mitochondrial respiration [154–156].

The chronic application of Al caused the accumulation of AβP in cultured neurons of rat cerebral cortex [64] and in neuroblastoma cells [65]. Praticó et al. (2002) found that orally administered Al caused a marked increase in the amount of AβP both in its secreted and accumulated forms, and increased deposition of senile plaques in AD-model mice transfected with the human APP gene (Tg 2576) [66]. These results are consistent with other studies demonstrating that oral Al exposure causes the accumulation of AβP and impairs spatial learning memory in AD-model mice [67].

Exposure to Al causes the accumulation of AβP and induces adverse effects in humans as seen in the aftermath of the accidental Al exposure in 1988 at Camelford [157]. The

neuropathological case study of a 58 year-old woman who was exposed to Al and died 15 years later with unspecified neurological symptoms demonstrated the rare form of sporadic cerebral amyloid angiopathy, which is characterized by the deposition of AβP in blood vessels and has a causative link with AD [158]. The deposition of high amounts of Al in the patient's brain was also observed.

Al has also been reported to bind and cause conformational changes in other AD-related proteins, including APP [138], tau protein [32, 57], and PHF-tau protein [139] and in proteins related to other neurodegenerative diseases such as α-synuclein (Parkinson's disease (PD) and dementia with Lewy bodies; DLB) [140, 141], amylin (diabetes mellitus) [142], ABri (familial British dementia) [143], and ataxin 3 (spinocerebellar ataxia type 3) [144], β_2-microglobulin (dialysis-related arthropathy) [145] (Table 2).

3.5. Metal-Metal Interactions in the Pathogenesis of AD. The evidence now suggests that the significance of Al in the pathogenesis of AD should be concerned. Other metals usually share the binding site of one metal ion, although their binding constants differ. Al binds to various metal-binding proteins and influences metal homeostasis. The interactions between Al and other metals should be considered owing to the implications of various trace elements in the pathogenesis of AD. Figure 5 illustrates the modified aluminum hypothesis that accounts for the implications of Al and other trace metals in AD pathology from the secretion of AβP to its neurotoxicity as mentioned below.

3.5.1. Al^{3+} Affects Iron-Homeostasis and Generates Free Radicals. Al has similar characteristics to iron (Fe) and binds to Fe-binding proteins such as ferritin, transferrin, iron regulatory protein (IRP) or to iron chelators such as DFO. The iron responsive element/iron regulatory protein (IRE/IRP) network regulates the production of iron binding proteins which prevent the formation of free Fe^{2+}, which causes toxic free radicals [159]. In iron-deficient conditions, IRP binds to IRE and regulates the expression of genes that contain IREs in their mRNA, such as ferritin or transferrin. As the concentration of free Fe^{2+} increases, the binding of iron to IRP, expression of transferrin is downregulated and that of ferritin is upregulated, and the amount of free Fe^{2+} is thereby decreased. Al^{3+} also binds to IRP [34, 160], and thus influences the expression of Fe-binding proteins with IREs in their mRNA causing an elevated Fe concentration [161]. Al also influences the uptake of iron into cultured neurons or glial cells [34, 162]. Thus, Al^{3+} affects iron homeostasis and the expression of various iron-regulated proteins with IREs. Important findings are that APP mRNA contains an IRE as well as ferritin, and its expression is regulated by iron [163]. Indeed, Al caused elevated expression of APP in experimental animals [40, 41]. Recently, Duce et al. demonstrated that APP has ferroxidase activity, which converts Fe^{2+} to Fe^{3+} and regulates free pro-oxidant Fe^{2+} concentrations [164]. They also found that Zn^{2+} inhibits the ferroxidase activity of APP. APP also possesses copper/zinc binding sites in its amino-terminal domain and in the AβP domain and may be involved in homeostasis of these metals [165]. Al^{3+} stimulates Fe-induced membrane lipid peroxidation and causes oxidative damage *in vitro* and *in vivo*, although Al^{3+} does not directly affect peroxidation [89, 90]. There are other important findings implicating iron homeostasis in AD pathogenesis. Iron related genes such as transferrin C2 or hemochromatosis were revealed to be risk factors for AD [166, 167]. Imagawa et al. (1992) reported that iron supplementation was effective for the recovery of cognitive functions in AD patients [168].

3.5.2. Al^{3+} and Other Metals Enhance the Oligomerization of AβP. An abnormal expression of APP could lead to an increased secretion of AβP, and then enhance its accumulation. Secreted AβP is usually degraded by various proteases such as neprilysin within a short period. The downregulation of neprilysin induced by Al can cause the accumulation AβP [43]. Furthermore, AβP becomes oligomerized in the presence of trace metals such as Al^{3+}, Zn^{2+}, Fe^{3+}, and Cu^{2+}, could be resistant to proteases, and thus accumulates in the brain.

3.5.3. Al^{3+} Impairs Calcium Homeostasis. AβP oligomers could be readily incorporated into cell membranes, resulting in the formation of ion channels [147]. A subsequent influx of Ca^{2+} through these amyloid channels would lead to the phosphorylation of tau, depletion of neurotrophic factors, and the formation of free radicals, and so forth, with the outcome of these effects being neuronal death. Al^{3+} blocks various Ca^{2+} channels and influences Ca^{2+} homeostasis. We found that Al also inhibits the increase in Ca^{2+} levels induced by brain-derived neurotrophic factor (BDNF) [94]. As described previously, Al is implicated in most of these neurodegenerative pathways such as dephosphorylation of tau [56], depletion of neurotrophic factor [38], formation of free radicals [89], and induction of neuronal death.

This working hypothesis may be useful in developing an understanding of the link between AD and trace elements including Al, Zn, Cu, and Fe. Considering the implications of metals in AD pathogenesis, chelation therapy for AD treatment is of great interest [169]. Clioquinol (quinoform), a chelator of Cu^{2+} or Zn^{2+}, inhibits oligomerization of AβP and attenuates the accumulation of amyloid in the brains of experimental animals. Clinical trials using its analogue PBT2 are under investigation [170]. DFO, a chelator of Al and Fe, attenuates the decline of daily living skills in AD patients [171]. Silicates, which couple with Al and reduce its toxicity, are also candidates for chelation therapy in AD [172].

4. Conclusion: Al and Human Health

In this review, we have summarized the properties associated with various aspects of Al neurotoxicity. There is growing evidence for a link between Al and AD, and between other metals and AD. Nevertheless, because the precise mechanism of AD pathogenesis remains unknown, this issue is controversial. However, it is widely accepted that Al is a recognized neurotoxin, and that it could cause cognitive deficiency

and dementia when it enters the brain and may have various adverse effects on CNS. In general, the absorption of metals by the gastrointestinal tract is widely variable and is influenced by various factors including an individual difference, age, pH, stomach contents [173]. Recent studies using mass spectrometry of ^{26}Al have demonstrated that small, but a considerable amount of Al crosses the blood brain barrier, enters into the brain, and accumulates in a semipermanent manner [174, 175]. Therefore, Al can cause severe health problems in particular populations, including infants, elderly people, and patients with impaired renal functions, and unnecessary exposure to Al should be avoided for such patients [176].

In 1989, a joint FAO/WHO Expert Committee on Food Additives (JECFA) recommended a provisional tolerable weekly intake (PTWI) of 7.0 mg/kg body weight Al; however, this was changed in 2007 to 1.0 mg/kg body weight because of potential effects on the reproductive system and the developing nervous system. The characteristics of Al neurotoxity are complex, and further research is needed especially in relation to bioavailability, cellular effects, metabolism, and metal-metal interactions.

Abbreviations

AD: Alzheimer's disease
AβP: β-amyloid protein
Al: Aluminum
ALS: Amyotrophic lateral sclerosis
APP: Amyloid precursor protein
BACE: β-APP cleaving enzyme
BDNF: Brain derived neurotrophic factor
CSF: Cerebrospinal fluid
CNS: Central nervous system
DFO: Deferoxamine
DLB: Dementia with Lewy bodies
JECFA: FAO/WHO Expert Committee on Food Additives
IRE: Iron responsive element
IRP: Iron regulatory protein
LAMMA: Laser microprobe mass analysis
LTP: Long-term potentiation
MAP: Microtubule-associated protein
NFT: Neurofibrillary tangle
NGF: Nerve growth factor
PD: Parkinson's disease
PHF: Paired helical filament

PTWI: Provisional tolerable weekly intake
TEM-EDX: Energy-dispersive X-ray spectroscopy combined with transmission electron microscopy.

Acknowledgments

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan and by a Grant from Cooperation for Innovative Technology and Advanced Research in Evolutional Area (CITY AREA) from the Miyazaki Prefectural Industrial Support Foundation.

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