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Review

Aluminum and Alzheimer's Disease: After a Century of Controversy, Is there a Plausible Link?

Lucija Tomljenovic*
Neural Dynamics Research Group, Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, BC, Canada

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Abstract. The brain is a highly compartmentalized organ exceptionally susceptible to accumulation of metabolic errors. Alzheimer's disease (AD) is the most prevalent neurodegenerative disease of the elderly and is characterized by regional specificity of neural aberrations associated with higher cognitive functions. Aluminum (Al) is the most abundant neurotoxic metal on earth, widely bioavailable to humans and repeatedly shown to accumulate in AD-susceptible neuronal foci. In spite of this, the role of Al in AD has been heavily disputed based on the following claims: 1) bioavailable Al cannot enter the brain in sufficient amounts to cause damage, 2) excess Al is efficiently excreted from the body, and 3) Al accumulation in neurons is a consequence rather than a cause of neuronal loss. Research, however, reveals that: 1) very small amounts of Al are needed to produce neurotoxicity and this criterion is satisfied through dietary Al intake, 2) Al sequesters different transport mechanisms to actively traverse brain barriers, 3) incremental acquisition of small amounts of Al over a lifetime favors its selective accumulation in brain tissues, and 4) since 1911, experimental evidence has repeatedly demonstrated that chronic Al intoxication reproduces neuropathological hallmarks of AD. Misconceptions about Al bioavailability may have misled scientists regarding the significance of Al in the pathogenesis of AD. The hypothesis that Al significantly contributes to AD is built upon very solid experimental evidence and should not be dismissed. Immediate steps should be taken to lessen human exposure to Al, which may be the single most aggravating and avoidable factor related to AD.

Keywords: Aging, aluminum, Alzheimer's disease, amyloidosis, bioavailability, brain compartmentalization, cholinergic dysfunction, G-proteins, neurofibrillary tangles, neurotoxicity

INTRODUCTION

Alzheimer's disease (AD) is a progressive form of dementia of the elderly and the most prevalent neurodegenerative disease in the world [1]. It is characterized by regional specificity of neural aberrations associated with higher cognitive functions in the hippocampus and neocortex [2–9]. Notably, such compartmentalized distribution of neural abnormalities is a main feature by which AD is distinguished from other forms of dementia, such as Huntington's, Parkinson's, and Wilson's diseases, which primarily involve neurological deficits affecting brainstem nuclei function [10]. Since its initial report in 1906, AD has reached global proportions and currently, it is one of the most burdensome and disabling health problems, affecting ∼24.3 million people [11]. More than 4.5 million new cases are diagnosed each year and it is predicted that by 2040 there will be

*Correspondence to: Lucija Tomljenovic, PhD, University of British Columbia 828 W, 10th Ave, Vancouver, BC V5Z 1L8, Canada. Tel.: +1 604 875 4111 (68373); E-mail: lucijat77@gmail.com.

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81.1 million people with AD [11]. A very small percentage of AD cases is inherited (familial AD, early onset of symptoms, <65 years), whilst >95% are idiopathic (late onset, >65 years) [1, 12, 13], and although several causative agents have been proposed, none is unambiguously proved nor ruled out [1, 3, 12, 14–20].

Depositions of amyloid β-protein precursor (AβPP)-derived amyloid-β (Aβ) fibrils, which form extracellular senile plaques (Fig. 1), and aggregates of hyperphosphorylated microtubule-associated protein (MAP) tau, which combines to form paired helical filaments (PHFs) within neurons (Fig. 2 [1, 12, 14]), are principal histopathological markers of AD [1, 12, 14]. However, it is not clear what triggers senile plaques and neurofibrillary tangles (NFT) formation in the absence of predisposing genetic susceptibilities. Furthermore, none of the alternative hypotheses that have been suggested thus far, including: 1) oxidative stress [17, 21], 2) dysregulation of calcium [12, 22, 23] and iron homeostasis [24–27], 3) deficits in microtubules (MTs [20]), 4) deficits in neurotransmission and G-protein-coupled receptor (GPCR) signaling [3–5, 8, 28], and 5) upregulation of neuroinflammatory signaling [16, 29], are able to explain the regional

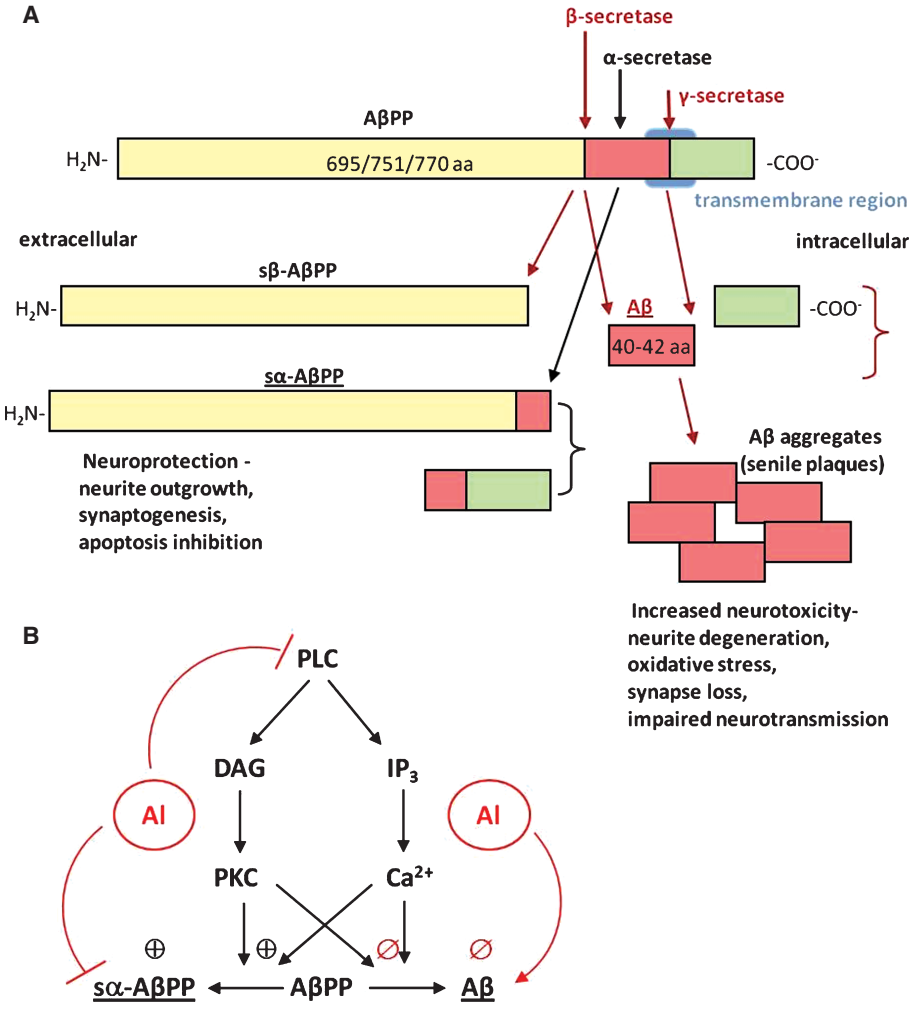

Fig. 1. Domain structure and processing of the AβPP. Panel A depicts the overall structure and cleaving sites for α-, β- and γ-secretases. AβPP is a type 1 trans-membrane protein that undergoes differential processing by two mutually exclusive pathways. Cleavage by α-secretase yields a neuroprotective soluble sα-AβPP and precludes the formation of the amyloidogenic neurotoxic $A\beta_{1\text{-}40/1\text{-}42}$ species which are produced by the sequential cleavage of β- and γ-secretase. There are several AβPP isoforms: $A\beta PP_{751}$ and $A\beta PP_{770}$ are glial-specific, while $A\beta PP_{695}$ is the predominant neuronal isoform [12]. Panel B shows two distinct mechanisms by which PLC regulates AβPP processing: PKC-dependent and Ca^{2+} dependent/PKC-independent (adapted from Buxbaum et al. [22]). Both pathways favor the formation of the neuroprotective sα-AβPP at the expense of the amyloidogenic Aβ species. Al promotes amyloidosis as it antagonizes the neuroprotective sα-AβPP pathway, by inhibiting agonist-stimulated PIP_2 hydrolysis by PLC and the formation of second messengers DAG and IP_3 (for further details see Fig. 2).

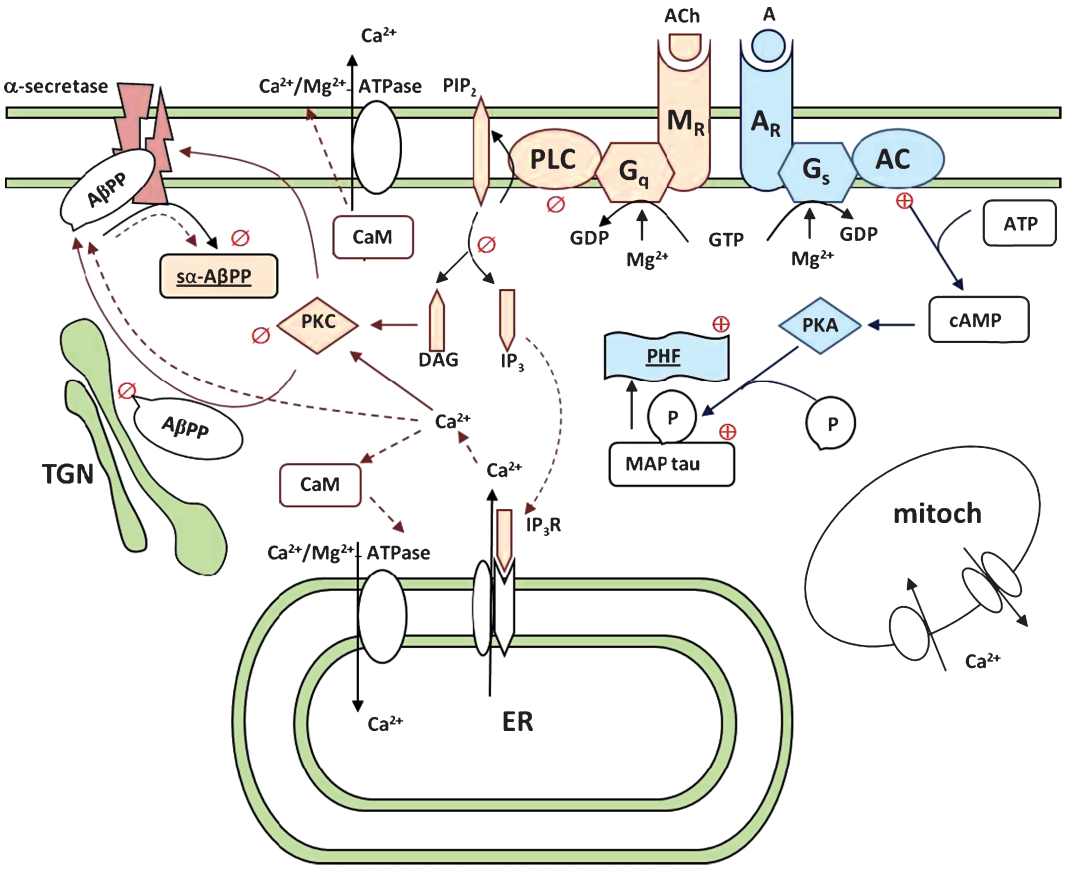

Fig. 2. Schematic illustration of 1) phospholipase C (PLC)/inositol 1,4,5-trisphosphate (IP_3) and 2) adenylate cyclase (AC)/cyclic AMP (cAMP) pathways. 1) Agonist (ACh) stimulation of cholinergic muscarinic receptors (M_R) promotes GDP to GTP exchange and activation of receptor-coupled G_q-proteins which activate PLC. Hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) by activated PLC yields two important signaling molecules: IP_3 and diacylglycerol (DAG). IP_3 stimulates release of Ca^{2+} from the ER and the mitochondria, and DAG, in concert with Ca^{2+}, activates protein kinase C (PKC). Ca^{2+} and PKC work by two separate mechanisms to stimulate the non-amyloidogenic pathway of AβPP processing by α-secretase, which results in production of the neuroprotective soluble AβPP (sα-AβPP). PKC promotes the budding of AβPP-containing secretory vesicles from the trans-Golgi network (TGN) and potentially targets α-secretase at the plasma membrane. Ca^{2+} activates calmodulin (CaM) which regulates the activity of the Ca^{2+}/Mg^{2+}-ATPases responsible for extrusion of cytosolic Ca^{2+}. 2) AC is activated by adrenergic receptor stimulation (A_R) and consequent activation of A_R-coupled G_s-protein via GDP to GTP exchange. Activated AC catalyzes ATP to form the second messenger cAMP which then activates protein kinase A (PKA). PKA phosphorylates microtubule-associated protein (MAP) tau on PKA-dependent serine residues. Hyperphosphorylated tau dissociates from the MTs and assembles into paired helical filament (PHF)-structures, main constituents of neurofibrillary tangles (NFT). Note that MAP tau has multiple phosphorylation sites but PKA-dependent serine phosphorylation is associated with increased formation of NFT in AD [225]. Al interferes with the PLC/IP_3 and AC/cAMP pathways in a biphasic manner, by negative and positive modulations (indicated ∅ and ⊕ respectively), and at multiple levels. By impairing M_R stimulated PIP_2 hydrolysis Al may promote both amyloidosis and cholinergic dysfunction. Note that acetylcholine (ACh) is a central neurotransmitter critical for higher cognitive functions and a classical activator of M_R receptors. Deficits in cholinergic signaling are a hallmark of AD and are reciprocated by Al. Conversely, by increasing cAMP, Al may induce the formation of NFTs.

specificity of neuronal degeneration, nor account for the subtle and persistent changes which over time result in progressive neural deterioration. Nor can these factors encompass the diversity of histological and molecular abnormalities observed in AD. While it is irrefutable that all of the aforementioned may be contributing events in AD, they cannot be instigated in the absence of either genetic predispositions or environmental triggers. Moreover, identical twin studies show that in 60% of cases, AD affects only one twin (the rate is similar for both monozygotic and dizygotic twins [30]), thus further underscoring the importance of environmental factors in the etiology of AD. Out of all bioavailable factors considered, aluminum (Al) is the only one that has been experimentally shown to trigger all major histopathological events associated with AD, at multiple levels (Table 1). It is also the most controversial proposed instigator [15, 31–36].

Table 1
Al's neurotoxic effects related to AD

Effects on memory, cognition and psychomotor control

Significantly decreases cognitive and psychomotor performance in humans and animals [10, 38, 39, 46, 48, 61, 63, 70, 87, 98, 165, 169, 170, 246, 248–253]

Impairs visuo-motor coordination, long-term memory, and increases sensitivity to flicker in humans and rats [169, 170]

Impairs memory and hippocampal long-term potentiation (LTP) in rats and rabbits *in vivo* (electrophysiological model of synaptic plasticity and learning [150, 254])

Effects on neurotransmission and synaptic activity

Depresses the levels and activity of key neurotransmitters known to decline in AD *in vivo*: acetylcholine, serotonin, norepinephrine, dopamine and glutamate [178, 255]

Reproduces hallmark cholinergic deficits observed in AD patients [3, 159, 160] by impairing the activity of cholinergic synthetic and transport enzymes:

- impairs acetylcholinesterase activity [256–258]
- reduces neural choline acetyltransferase [158–160, 255]
- inhibits choline transport in rat brain [159, 259] and in synaptosomes from cortex and hippocampus [219]
- attenuates acetylcholine levels in rabbit hippocampus and concomitantly induces a learning deficit [63]
- may cause acetylcholine deficit by acting upon muscarinic receptors and potentiating the negative feedback controlling acetylcholine release into the synaptic cleft [6]

Inhibits neuronal glutamate-nitric oxide (NO)-cyclic GMP (cGMP) pathway necessary for LTP [260]

Damages dendrites and synapses [2, 70, 165, 261]

Impairs the activity of key synaptosomal enzymes dependent on Na-K, Mg^{2+} and Ca^{2+} [262]

Inhibits glutamate, GABA and serotonin uptake into synaptosomes [64, 263]

Impairs neurotransmission by disrupting post-receptor signal transduction mediated by the two principal G-protein regulated pathways: PLC and AC (see Effects on G-proteins and Ca^{2+} homeostasis)

Inhibits dihydropteridine reductase, essential for the maintenance of tetrahydrobiopterin (BH4), a cofactor important in the synthesis and regulation of neurotransmitters [264]

Impairs ATP-mediated regulation of ionotropic and metabotropic receptors-cholinergic, glutamatergic and GABAergic [6]

Interferes with receptor desensitization by increasing the stability of the metal-ATP receptor complex and causes prolonged receptor activity (by replacing Mg^{2+} from the metal site) [6]

Effects on G-proteins and Ca^{2+} homeostasis

Alters IP and cAMP signaling cascades by interfering with G-proteins (as AlF), second messengers and second messenger/Ca^{2+} targets [6, 77–79, 147, 167, 219, 265, 266]:

- potentiates agonist-stimulated cAMP production following chronic oral exposure in rats, by inhibiting the GTPase activity of the stimulatory G protein (G_s), leading to prolonged activation of G_s after receptor stimulation and increased cyclic AMP production by AC [167]
- increases cAMP levels by 30–70% in brains of adult and weanling rats [167]
- inhibits muscarinic, adrenergic and metabotropic receptor-stimulated IP_3 accumulation by inhibiting G_q-dependent hydrolysis of PIP_2 by PLC [147, 219, 265, 266]
- decreases IP_3 in the hippocampus in rats following chronic oral administration [167]
- inhibits PKC [147, 265, 267]
- blocks the fast phase of voltage-dependent Ca^{2+} influx into synaptosomes [268]
- binds to CaM and interferes with numerous CaM-dependent phosphorylation/dephosphorylation reactions [146, 151, 269]
- impairs Ca^{2+}/CaM dependent LTP [150, 260]

May cause a prolonged elevation in intracellular Ca^{2+} levels by:

- interfering with desensitization of the N-methyl D-aspartate (NMDA) receptor channel [6]
- delaying the closure of voltage-dependent Ca^{2+} channels [6] and
- blocking CaM-dependent Ca^{2+}/Mg^{2+}-ATPase responsible for extrusion of excess intracellular Ca^{2+} [6, 148, 150]

Elicits a Ca^{2+}-dependent excitotoxic cascade by frequent stimulation of the NMDA receptor which may result in:

- persistent further activation of NMDA receptor by endogenous glutamate and exacerbation of glutamate excitotoxicity [50, 137, 270]
- mitochondrial and ER Ca^{2+} store overload [6]
- compromised neuronal energy levels [271]
- erosion of synaptic plasticity [6]
- increased susceptibility to apoptosis and accelerated neuronal loss [6, 50, 271]

Perturbs neuronal Ca^{2+} homeostasis and inhibits mitochondrial respiration in a complex with amyloidogenic Aβ peptide in a triple transgenic mouse model of AD [271]

Metabolic and inflammatory effects

Inhibits utilization of glucose in the brain [146, 219]

Inhibits hexokinase and G6PD [19, 146, 154]

Reduces glucose uptake by cortical synaptosomes [272]

Alters Fe^{2+}/Fe^{3+} homeostasis [19, 152, 205] and potentiates oxidative damage via Fenton chemistry [19, 137, 209, 211, 212]

Table 1
(*Continued*)

Alters membrane properties by:
- decreasing the content of acidic phospholipid classes: phosphatidylserine (PS), phosphatidylinositol (PI) and phosphatidic acid (PA) in rat brain myelin by 70% [216]
- inducing the clustering of negatively charged phospholipids, thereby promoting phase separation, membrane rigidification and facilitating brain-specific LPO [212]

Increases the permeability of the BBB by:
- increasing the rate of trans-membrane diffusion [163] and
- selectively changing saturable transport systems [27, 68, 163, 175]

Facilitates glutamate transport across the BBB and potentiates glutamate excitotoxicity [50, 133–135, 137]
Decreases antioxidant activity of SOD and catalase in the brain [164]
Increases cerebellar levels of nitric oxide synthase (NOS) [232]
Augments specific neuro-inflammatory and pro-apoptotic cascades by inducing transcription from a subset of HIF-1 and NF-κB – dependent promoters (AβPP, IL-1β precursor, $cPLA_2$, COX-2 and DAXX [70, 209, 237])
Activates microglia, exacerbates inflammation and promotes degeneration of motor neurons [87, 273]

Nuclear effects

Binds to phosphonucleotides and increases the stability of DNA [236]
Binds to linker histones, increases chromatin compaction, depresses transcription [65, 157, 174, 182–185]
Inhibits RNA polymerase activity [155–157]
Reduces the expression of the key cytoskeletal proteins α-tubulin and β-actin [155, 274]
Downregulates the expression of the light chain of the neuron-specific neurofilament (NFL) gene in 86% of surviving neurons in the superior temporal gyrus of AD patients [184]
Up-regulates well known AD-related genes: amyloid precursor-like protein (APLP)-1 and APLP-2, tau and AβPP, in human neuroblastoma cells when complexed with Aβ, to a larger extent than other Aβ-metal complexes (Aβ-Zn, Aβ-Cu and Aβ-Fe) [14]
Up-regulates HIF-1 and NF-κB – dependent gene expression (see Metabolic and inflammatory effects)

Effects on MTs, cytoskeleton and NFT formation

Induces neurofibrillary degeneration in basal forebrain cholinergic neurons [43], cortical and hippocampal neurons [43, 49, 59, 220, 253, 255] and accumulates in NFT-bearing neurons [42, 46, 47, 275]
Causes neurite damage and synapse loss in hippocampal and cortical pyramidal neurons by disabling their capacity for MT assembly [2, 70]
Directly alters MT assembly by interfering with magnesium and GTP-dependent MT-polymerization mechanisms. Actively displaces magnesium from magnesium-binding sites on tubulin and promotes tubulin polymerization [147, 149, 276]
Decreases the sensitivity of MTs to calcium-induced depolymerisation and effectively disables the regulatory circuits that are set to maintain the sensitive dynamics between polymerization and depolymerisation cycles of tubulin, and ultimately, impairs MT assembly [20, 149]
Inhibits axonal and dendritic transport mechanisms by depleting MTs [10]
Induces cAMP-dependent protein kinase phosphorylation of MAPs and NFs in rats following chronic oral exposure [167] and enhances the formation of insoluble NF aggregates [250, 274, 277]. Al-induced hyperphosphorylated NFs are resistant to dephosphorylation and degradation by calcium-dependent proteases (calpain) [277]
Promotes highly specific non-enzymatic phosphorylation of tau *in vitro* by catalysing a covalent transfer of the entire triphosphate group from ATP to tau via O-linkage (cAMP-dependent protein kinase phosphorylation sites [225]), at concentrations similar to those reported in AD brains [162, 227]
Induces tau phosphorylation and motor neuron degeneration *in vivo* (as a vaccine adjuvant [87])
Facilitates cross-linking of hyperphosphorylated tau in PHFs, stabilizes PHFs and increases their resistance to proteolysis [45, 278, 279]
Inhibits dephosphorylation of tau in synaptosomal cytosol fractions [280]
Decreases levels of specific MAP isoforms [168]

Effects on amyloidosis

Elevates AβPP expression and induces senile plaque deposition in 30% of patients subjected to chronic dialysis treatment [44]
Elevates AβPP expression, promotes Aβ deposition and amyloidosis in hippocampal and cortical pyramidal neurons in rats and mice following chronic oral exposure [70, 82, 83, 231]
Binds the amyloidogenic Aβ peptide and perturbs its structure from a soluble α-helical form to the insoluble random turn β-sheet conformation at physiologically relevant concentrations [281, 282]. The neurotoxic Aβ-sheet conformation may be reversed by the addition of a natural Al binder-silicic acid, a promising therapeutic agent for AD [37, 283]
Promotes the formation of amyloid fibrils in complex with ATP [284] and induces their aggregation [285]
Induces conformational changes in Aβ and enhances its aggregation *in vitro* in cultured mouse cortical neurons, following chronic (50 μM, >3 weeks) but not acute exposure (10–100 μM, 1 week [285])
Appears to be the most efficient cation in promoting $A\beta_{1\text{-}42}$ aggregation and potentiating $A\beta_{1\text{-}42}$ cellular toxicity in human neuroblastoma cells:
- induces a specific oligomeric state of $A\beta_{1\text{-}42}$ and by stabilizing this assembly markedly reduces cell viability and alters membrane structure, an effect not seen with other metal complexes ($A\beta_{1\text{-}42}$-Zn, $A\beta_{1\text{-}42}$-Cu and $A\beta_{1\text{-}42}$-Fe) or $A\beta_{1\text{-}42}$ alone [14, 286]
- strongly enhances the spontaneous increase of $A\beta_{1\text{-}42}$ surface hydrophobicity (compared to $A\beta_{1\text{-}42}$ alone, $A\beta_{1\text{-}42}$-Zn, $A\beta_{1\text{-}42}$-Cu and $A\beta_{1\text{-}42}$-Fe), converting the peptide into partially folded conformations [14, 286]

Table 1
(*Continued*)

May promote amyloidosis by interfering with the muscarinic acetylcholine receptor-stimulated IP_3/PLC-regulated production of the neuroprotective nonamyloidogenic sα-AβPP (Fig. 2 [4, 8, 22, 241, 287, 288]):
as fluoroaluminate, blocks DAG/PKC-dependent budding of secretory vesicles containing AβPP from the trans-Golgi network (TGN), thus inhibiting AβPP redistribution towards the plasma membrane where it would undergo processing by α-secretase to produce sα-AβPP [289]
may inhibit IP_3/Ca^{2+} – dependent production of sα-AβPP [22, 288]
may inhibit PKC-dependent AβPP cleavage by α-secretase [289, 290]
Inhibits proteolytic degradation of Aβ by cathepsin D [291]

There are many unresolved questions about Al bioavailability. This perhaps leads to erroneous conclusions regarding the significance of Al in the pathogenesis of AD. This review elucidates how: 1) the brain's inherent structural and functional heterogeneity provides a basis for differential susceptibility of specific cellular systems to Al neurotoxicity and 2) how Al's active sequestration of specific systemic transport mechanisms results in its compartmentalized distribution within the brain in a pattern that strongly implicates its role in AD. Special emphasis is given to Al's chemical and physical properties and their relevance to the etiology of AD.

ALUMINUM AND AD: WHY IS THERE A DEBATE?

Al, the third most abundant element on earth (after oxygen and silicon [37–40]), has been demonstrated in the literature to be a neurotoxin (Table 1). It is widely bioavailable to humans (Tables 3–5) and known to accumulate at higher concentrations in brain regions that are selectively affected in AD, including the entorhinal cortex (an area that shows the earliest pathological changes in AD), hippocampus, and the amygdala [2, 41–48]. Pyramidal cells in the hippocampus and cortex, basal forebrain cholinergic neurons, and upper brainstem catecholaminergic neurons associated with higher cognitive functions are the most affected neuronal populations in AD and also, the most susceptible to Al-induced neurofibrillary degeneration [10, 43, 47, 49, 50]. A strong association of Al with NFTs in AD was first observed by Perl and Brody [42], who used a combination of scanning electron microscopy and X-ray spectrometry, which enabled them to assess the localization of Al in brain biopsies at cellular and subcellular levels. Al foci were explicitly found within the nuclear regions of NFT-bearing neurons in the hippocampi from AD patients as well as non-demented elderly controls, while they were absent from adjacent healthy neurons from both groups of patients. Perl and Brody's observations were later confirmed by Andrasi et al. [51] using more sophisticated method (which eliminated the interfering reaction of phosphorous) and were also experimentally reproduced by Uemura [52] in an animal model of Al-induced neurofibrillary degeneration. Contrary to previous experiments, Uemura [52] was one of the first to examine the effects of chronic administration of Al in animals (administered subcutaneously over a period of either 40 or 90 days, rather than as a single intracerebral sub-lethal dose). Using a similar X-ray microprobe approach as Perl and Brody, Uemura [52] found elevated levels of Al within the nucleus of a high percentage of NFT-bearing neurons in the spinal cord and hippocampus. Also in concordance with Perl and Brody's results, Al was not detected in NFT-free neurons.

In spite of these observations, the causative role of Al in AD has been disputed, as some researchers failed to detect elevated levels of Al in AD brains despite using highly sophisticated and sensitive detection methods [53, 54]. These discrepancies fuelled further criticism about the Al-AD hypothesis and were further bolstered by the fact that Al has no biological essentiality, appears to be both poorly absorbed and efficiently excreted from the body [38–40, 55–57] and presumably, cannot accumulate in brain tissue in sufficient amounts to cause damage under physiologically relevant conditions [38, 40]. The presence of Al in the brain was subsequently attributed to experimental artifacts [54] or to passive uptake by dysfunctional neurons [58]. Furthermore, although Al-induced dialysis encephalopathy in chronic renal failure patients and intracerebral injection of a lethal threshold doses of Al in experimental animals results in development of neurofibrillary-like tangles, these lesions are less common and/or show distinct cellular topology and morphology from those in AD (although they are immunochemically similar to classical NFTs; Table 2). Similarly, the frequent occurrence of seizures, rapid progression, and severity of neuropathological abnormalities associated with Al-induced neurofibrillary degeneration in dialysis patients and experimental

Table 2
Comparisons between AD, dialysis dementia and animal models of neurofibrillary degeneration and amyloidosis

	AD	Dialysis dementia	Early animal models of neurofibrillary degeneration	Recent animal models of AD and AD-like amyloidosis
Duration and outcome	Fatal within 18 months–27 years (average 10 years) [10]	Fatal within 3–7 months following onset of symptoms unless treated (DFO and reverse osmosis to remove Al salts from the water used to prepare the dialysis fluid) [57, 180, 248, 252]	Fatal unless treated with anti-epileptic medications, treated animals survive but with persistent neurophysiological deficits [246]	Aged rats and mice are normally sacrificed following exacerbation of symptoms [70]
Symptoms	Gradual and steady decline in mental abilities appearing first in memory and later in speech and psychomotor control, behavioral changes including paranoia, depression, delusions and hallucinations [1, 10]	Symptoms appear suddenly and worsen either during or immediately after a dialysis session [248, 252, 292–294]. The first symptom to appear is a speech abnormality, then tremors, impaired psychomotor control, memory losses, impaired concentration, behavioral changes, epileptic seizures, coma and death [57, 248, 252, 292–294]	Decline in memory, impaired learning responses, deterioration in psychomotor control, epileptic seizures and death [220, 250, 253, 295–298]	Memory deficits and impaired performance in learning tasks, impaired concentration, behavioral changes including confusion and repetitive behavior [48, 61, 70, 165, 169]
Age of onset	Idiopathic AD (95–99% prevalence) >65 years [1, 13] Familial AD (1–5% prevalence) <65 years [1, 13]	Depending on duration of dialysis treatment, generally in patients who have been undergoing dialysis for 2–7 years [248, 252, 294]. Flendrig et al. [252] reported 6 cases of dialysis dementia, the youngest patient was 15 years and the rest were between 39–61 years of age when they died	7–10 days after injection [220, 296]	At human equivalent, in Al-treated rats generally by 27 months [2, 48, 61, 70, 82, 83] in AlF-treated rats by 15 months [82, 83]. In transgenic mice by 12 months [231]. Adult rats are generally maintained on an low Al-supplemented diet throughout life [2, 48, 61, 70, 82, 83] and mice for 12 months [231]
Amyloid/senile plaques	Common [1, 12–14, 16, 18]	Detected in 30–50% of patients [44, 45]	Uncommon	Uncommon [2, 70, 82, 83, 231] typical extracellular senile plaques are species-specific and do not normally develop in rodents [70] but AβPP accumulation is observed in affected dendrites and axons [70, 299] and Aβ in cerebral vessels [82] Common in AβPP transgenic mice [231]
NFTs	Common, composed of paired helical filaments (PHFs) [1, 7, 14, 20, 47, 225, 275, 279]	Uncommon [44], but when present, composed of PHFs [45]	Common but morphologically and topologically distinct from those in AD (due to species-specific differences), composed of straight filaments [298, 300, 301]. Nonetheless, both share the immunoreactivity for phosphorylated tau and NF proteins [302–304]	Uncommon in rats but their main component, hyperphosphorylated tau, is common [305]

Table 2
(*Continued*)

	AD	Dialysis dementia	Early animal models of neurofibrillary degeneration	Recent animal models of AD and AD-like amyloidosis
Al source	Dietary, environmental, lifestyle (vaccines, cosmetics, pharmaceuticals, processed foods antiperspirant etc.; see Tables 3–6)	Primary source: intravenously-administered dialysis fluid (derived from Al-treated tap water [57, 251, 252]). There were no incidences of dialysis dementia prior to introduction of Al salts in water supplies [251, 252] Secondary source: Al containing oral medications [294]	Intracerebral injection of a sub-lethal Al dose [220, 253, 295, 297]	Dietary, either in food or water [2, 48, 61, 70, 82, 83, 165, 178, 231]
Al brain burden	Non-demented controls: 0–2 μg/g dry weight [275, 306] AD: 3–4 × the control level (3–7 μg/g dry weight) [41, 49, 275]	10–15 × the control levels (23 μg/g dry weight) [59, 247, 248, 306]	Similar to AD: 4–6 μg/g dry weight [49, 246, 253, 275]	2 × the control level >2.5 μg/g dry weight [82]
Al localization – cellular and subcellular	NFTs, amyloid plaques, neuronal nuclei, throughout cells, perinuclei and granulovacuolar degeneration [42, 47, 59, 174, 247, 307]	Generally, uniform [59]	NFTs, neuronal nuclei [59]	Neuronal nucleoli, nuclei, throughout cells, granulovacuolar degeneration [70, 82, 83, 231, 305]
Al localization – tissue	Largely restricted to specific compartments of the brain-hippocampus, cortex [41, 46, 47, 49, 247, 296]	In the brain: focal accumulations are sometimes observed in the hippocampus and cortex [44, 173]. In other tissues: primarily bone and red blood cells, giving rise to bone disease-osteomalacia (or renal osteodystrophy) and microcytic anemia [56, 57, 179, 180, 308]. Parathyroid gland, joints, lung, heart, liver, spleen, muscle, skin and hair may also be affected [56, 179, 180, 252]	May depend on the site of injection [301]	Largely restricted to specific compartments of the brain-hippocampus, cortex, red blood cells, kidney tubules [2, 48, 70, 82, 83, 165, 231]
Reversal by DFO	Partially effective, slows down progression but does not reverse AD [60]. Recent experiments show that a combination of two Al chelators, ascorbate and Feralex-G, is effective in removing Al from the nuclei and hence a potentially useful pharmacotherapeutic approach to AD [278, 309]	Effective [180, 310, 311]	NFTs reversed by DFO in rabbit brains [302]	–

animals, contrasts with the insidious and latent development of neurological deficits in AD (Table 2). Moreover, brain biopsy samples show that in spite of high overall Al brain burden, intranuclear Al is not significantly elevated in dialysis dementia patients [59]. Finally, while chelating Al by desferrioxamine (DFO), successfully reverses dialysis dementia, it is less effective in improving the clinical outcome of AD (Table 2) [60]. Taken together, these discrepancies have been historically used to dismiss the significance of Al toxicity in AD.

Nonetheless, such dismissals may not be warranted as it is well known that the severity and clinical outcome of metal intoxication primarily depends on the dose, route, and duration of exposure as well as species differences. Al is no exception [6, 61–64]. In addition, intranuclear Al is particularly resistant to removal by chelating agents [65], and this most likely accounts for decreased responsiveness to DFO treatment in AD patients. Furthermore, a possible explanation for the absence of widespread neurofibrillary tangle-like pathology in dialysis patients which is so typical of AD, as well as animal models of Al-induced neurofibrillary degeneration (Table 2), may be the presence of oxygenated metabolites capable of binding Al and modifying its toxic action. Such metabolites would be expected to accumulate in abnormal amounts due to chronic renal failure [15]. Noteworthy, the significance of Landsberg et al. [54, 66] work is questionable due to a number of inconsistencies for which no adequate explanation is provided. For example, Landsberg et al. produced a subsequent paper in 1993 in which they were able to detect Al in plaques of AD brains [66], contrary to their widely cited precedent study [54]. This is despite the fact that their detection method in the former experiment was stated as being three times more sensitive. Nonetheless, they suggest that Al presence in stained plaques was due to a contamination of a staining solution [66]. In addition, Landsberg et al. provided no data in regards to the elemental content on NFTs [54, 66] where Al is known to accumulate in high amounts and concluded that Al does not have a role in AD. Resolving this dilemma, Walton et al. [67] used ^{26}Al isotope and ultra sensitive accelerator mass spectrometry (AMS) which enabled them to study Al toxicokinetics at physiologically relevant levels of Al exposure in rats (^{26}Al can be quantified by AMS with extreme sensitivity, $\sim 1 \times 10^6$ atoms as the $^{26}\text{Al}:{}^{27}\text{Al}$ ratio [33, 68, 69]. Their results showed that trace amounts of Al from the equivalent of a single glass of water readily entered the brains of rats [67], thereby providing the most compelling evidence to date against the hypothesis that the accumulation of Al in neurons is an artifact.

Finally, it should be fairly obvious that AD does not result from a direct intracerebral injection of a sub-lethal dose of Al routinely used in animal models of neurofibrillary degeneration, nor sub-acute intravenous exposure commonly associated with dialysis dementia (Table 2). Accordingly, the prolonged clinical course of AD is suggestive of a chronic life-long exposure to low doses of a neurotoxicant such as Al [6, 48]. Consistent with this and more relevant to human exposure, recent studies by Walton [2, 48, 70] show that chronic ingestion of Al in rats, in amounts equivalent to those humans routinely ingest, results in neuropathological outcomes characteristic of AD, including cognitive deterioration, hippocampal, and cortical increases in AβPP expression and deposition and higher Al content in the perikarya of pyramidal cells. Walton's work [2, 48, 70] demonstrates how small doses of a known neurotoxicant can accumulate over lifetime in sufficient amounts to trigger a neurodegenerative disease in otherwise healthy animals with no obvious genetic predispositions.

BIOAVAILABLE ALUMINUM

As noted by Exley et al. [37] "*In the absence of recent human interference in the biogeochemical cycle of aluminium the reaction of silicic acid with aluminium has acted as a geochemical control of the biological availability of aluminium.*" Unlike manufactured Al compounds (such as food additives), naturally occurring compounds such as aluminosilicates (essential components of rock and soil minerals) are poorly absorbed and insoluble at neutral pH [38–40]. Al easily transits from solid to liquid phase at low pH values, and is quickly mobilized by acid rain which results in its accumulation in plants and natural water systems [38, 39, 57, 71, 72]. Surface waters have naturally a much higher Al content than ground waters [57, 73]. Notably, human exposure to Al was rather limited up until late 1880s, when Al production increased for industrial and commercial purposes [74]. Thereafter, Al salts were introduced in rapid water filtration systems for water purification purposes, to reduce organic matter, turbidity, and microorganisms [71]. Al sulfate is the most commonly used flocculant [39, 71], thought to reduce particulate forms of Al (and this presumably decreases the total Al water content). However, flocculation by Al sulfate frequently increases the levels of the more toxic soluble monomeric inor-

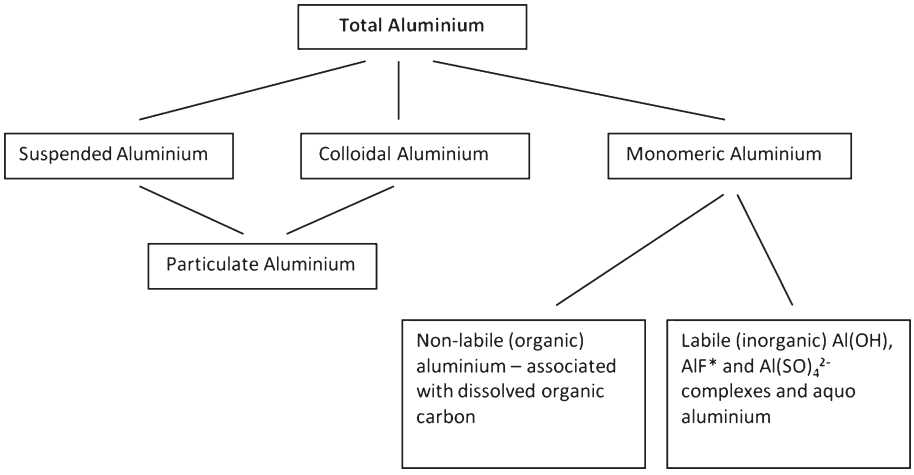

Fig. 3. Al fractions in water. Note that AlF increasingly forms in fluoridated potable supplies. Adapted from Srinivasan et al. [317].

ganic forms in the finished water (Fig. 3) [39, 75, 76]. Interestingly, during a survey of 186 randomly selected community water supplies in the USA, Miller et al. [73] noted that there was a 40 to 50% chance that the total Al content in the finished water (0.014–2.67 mg Al/L) would be above the original content of un-treated natural water (0.014–0.29 mg Al/L ground water and 0.016–1.17 mg Al/L surface water). Noteworthy, in certain cases Al-treated water had more than double the Al content of the naturally more contaminated surface water (2.67 vs 1.17 mg Al/L) [73]. Of significant concern is the presence of potentially extremely toxic fluoroaluminates ($AlF^{-}{}_{x}$), which form in aqueous solutions containing fluoride anions and trace amounts of Al [39, 77]. These complexes act as structural analogues of PO_4^{3-} in cellular signaling cascades and have the potential to cause numerous adverse systemic effects in humans [77–81]. Furthermore, fluoroaluminates are easily transported across the blood brain barrier (BBB), and in rats, chronic dietary exposure to $AlF^{-}{}_{x}$ complexes causes severe damage to cerebrovascular endothelia and neurons, in a region-specific manner reminiscent of AD [82, 83]. The enhanced toxicity in the fluoroaluminate group (compared to that treated with sodium fluoride), resulted from the ingestion of an additional 0.1 mg Al/kg bw/day [82]. From these observations it is evident that in the presence of fluoride, only trace amounts of Al are needed to produce substantial neuronal injury. Both fluoride and Al when complexed in $AlF^{-}{}_{x}$ appear to be more easily absorbed from the gastrointestinal (GI) tract compared to their ionic forms [39, 82, 83]. In spite of these observations, water fluoridation persists in USA, Canada, Australia, and New Zealand while most of Europe has abandoned this practice [77, 84]. Of note, contrary to World Health Organization (WHO) predictions, the incidence of dental caries has decreased significantly after the suspension of water fluoridation in Japan and many European countries [84]. In fluoride-treated water, fluoroaluminates are the prevalent species [39]. The enhanced transport of fluoroaluminates across the GI tract and the BBB, in context to their highly neurotoxic potential, raises significant concerns about the prevalence of these compounds in drinking water of various countries [82, 83].

The first case of AD was reported in Frankfurt ∼20 years following the expansion in use of Al products "*The case presented even in the clinic such a different picture, that it could not be categorised under known disease headings, and also anatomically it provided a result which departed from all previously known disease pathology*" (Dr Alois Alzheimer) [85]. Alzheimer's astute observations were later supported by a report in Lancet, which affirmed AD as a rare condition (by 1926, a total of 33 cases of AD have been confirmed) [86]. Al is now widespread, AD affects ∼24.3 million of the world's population (a new case is diagnosed every 7 seconds) [11], and most people are unaware of their chronic routine exposure to Al compounds (Tables 3–6). Al is present in natural as well as processed foods, beverages, pharmaceuticals, vaccines, cosmetics, and many modern life-style utilities (Tables 3–5) [38, 39, 72, 87–98].

Since 1989 a considerable number of studies have related elevated Al levels in water to an increased risk of cognitive impairment and Alzheimer-type dementia [99–105], especially in conditions of low silica content [102, 104, 106]. Recently Campbell et al. [107]

Table 3
Estimates of daily and weekly intakes of Al in humans

Major sources of Al exposure in humans	Daily Al intake (mg/day)	Weekly Al intake (mg/day)	÷ PTWI[†] (1 mg/kg/bw; for an average 70 kg human PTWI = 70 mg)	Amount delivered daily into systemic circulation (at 0.25% absorption rate)
Natural Food	1–10 [38, 195]	7–70	0.1–1	2.5–25 μg
Food with Al additives	1–20 (individual intake can exceed 100) [89, 109]	7–140 (700)	0.1–2 (10)	2.5–50 μg (250 μg)
Water	0.08–0.224 [38, 195]	0.56–1.56	0.008–0.02	0.2–0.56 μg
Pharmaceuticals (antacids, buffered analgesics, anti-ulceratives, anti-diarrheal drugs)	126–5000 [38, 88, 195]	882–35,000	12.6–500	315–12,500 μg
Vaccines (HepB, Hib, Td, DTP)	0.51–4.56 [312]	NA	NA	510–4560 μg [‡]
Cosmetics, skin-care products and antiperspirants [§]	70 [88, 312]	490	NA	8.4 μg (at 0.012% absorption rate [118, 313])
Cooking utensils and food packaging	0–2 [38]	0–14	0–0.2	0–5 μg

[†] PTWI (Provisional Tolerable Weekly Intake) is based on orally ingested Al, generally only 0.1–0.4% of Al is absorbed from the GI tract, however, Al may form complexes with citrate, fluoride, carbohydrates, phosphates and dietary acids (malic, oxalic, tartaric, succinic, aspartic and glutamic), which may increase its GI absorption (0.5–5% [38, 39]). Co-exposure with acidic beverages (lemon juice, tomato juice, coffee) also increases Al absorption as well as conditions of Ca^{2+}, Mg^{2+}, Cu^{2+} and Zn^{2+} deficiency [38, 57, 178, 195].

[‡] A single dose of vaccine delivers the equivalent of 204–1284 mg orally ingested Al (0.51–4.56 mg), all of which is absorbed into systemic circulation [117, 118]. Al hydroxide, a common vaccine adjuvant has been linked to a host of neurodegenerative diseases, it also induces hyperphosporylation of MAP tau in *vivo* [87, 129, 314].

[§] The risk of antiperspirants is both from dermal exposure and inhalation of aerosols. Inhaled Al is absorbed from the nasal epithelia into olfactory nerves and distributed directly into the brain [118, 313].

have validated concerns over Al in drinking water by demonstrating that exposure to low levels of Al lactate (0.01, 0.1, and 1 mM) in drinking water for 10 weeks increased inflammatory processes selectively in the brains of mice (as no parallel changes were observed in the serum or liver of treated animals). The authors noted that the lowest of these levels are in the range found to increase the prevalence of AD in regions where the concentrations of the metal are elevated in municipal drinking water [108]. Nonetheless, as pointed out by Rogers and Simon [91] (authors of the sole study that assessed the role of dietary Al in relation to AD), they have all ignored one of the most important sources of Al for an average citizen: food (representing ∼95% of the daily oral intake) [88]. Although average estimates of total daily intakes vary between 2 and 25 mg Al/day (14–175 mg/week) [38, 89, 94, 109], individual intake in urban societies can easily exceed 100 mg/day (700 mg/week; Table 3) due to a widespread increase in consumption of processed convenience foods which are typically high in Al-containing additives (Table 4). In 2006, the Food and Agriculture (FAO) WHO Expert Committee amended their provisional tolerable weekly intake (PTWI) for Al from 7 mg/kg/bw (490 mg/week, for an average 70 kg human) to 1 mg/kg/bw (70 mg/week) [110]. The Committee concluded that "*aluminum compounds have the potential to affect the reproductive system and developing nervous system at doses lower than those used in establishing the previous PTWI and therefore revised the PTWI*" [110]. The take home message is that a large proportion of people are unwittingly consuming significantly more Al than what is considered safe by the expert food authorities (Tables 3 and 5).

Of particular concern is exposure to Al in children through diet and vaccination programs. Infants are at particular risk, as are all those under 5 years of age, since the BBB in young children is immature and more permeable to toxic substances [38, 110, 111]. Unfortunately, these are also the groups that obtain most Al from both of the aforementioned sources (Tables 5 and 6). According to the latest vaccination schedule, every child in the USA will receive a total of 5–6 mg of Al by the age of 2 years, or up to 1.475 mg of Al during a single visit to the pediatrician (Table 6). This is contrary to the upper limit of 5 μg Al/kg/day set by the Food and Drug Administration (FDA) for premature neonates and individuals with impaired

Table 4
Foods and pharmaceuticals with highest and lowest Al content

	mg Al/serving	mg Al/kg mg Al/L (beverages)
Pharmaceuticals (1 tablet or 5 mL liquid)		
Antacids	35–208 [38]	
Buffered aspirin	9–52 [38]	
Anti-ulceratives	35–1450 [38]	
Anti-diarrheal drugs	207 [38]	
Beverages†		
Tea (natural)	0.1–0.73 (250 mL)	0.424–2.931 [38]
Soft drinks	0.02–0.52 (250 mL)	0.103–2.084 [38]
Foods†		
Natural unprocessed foods	0.15–0.7 (30–150 g)	<5 [38, 39]
Ready to eat pancake, waffle mixes	52–182 (120–140 g)	430–1280 [89]
Cheese, processed	11.5–40 (28 g)	411–1440 [88, 89]
Cornbread	18 (1 piece, 45 g)	400 [130]
Tortillas	3.9 (1 medium, 30 g)	129 [130]
Muffins	5.1 (1 muffin, 40 g)	128 [130]
Miscellaneous		
Baking powder (containing SALP‡)	20–30 (∼1 g)	20,000–28,000 [89]
Non-dairy creamer	0.1–1.5 (2–3 g)	50–600 [89]
Table salt (with Al-anticaking agents)	0.1–0.2 (∼1 g)	125–195 [89]
Herbs and spices (natural)	<0.05 (∼1 g)	3.74–56.50 [38]
Infant formulas		
Soy-based	0.5 (200 mL)	up to 2.5 [38, 315]
Milk-based	0.012–0.03 (200 mL)	0.06–0.15 [38]
Mother's milk	0.002 (200 mL)	<0.05 [38]

† Most natural foods have <5 mg Al/kg with some exceptions such as herbs, spices and tea, however, Al in tea may be bound to polyphenolic compounds and poorly absorbed [88, 177].
‡ SALP-acidic sodium Al phosphate.

kidney function [112]. Healthy neonates may be able to handle more Al, however, there are no such studies available upon which we could safely estimate acceptable upper levels of Al from parenteral or injectable sources in healthy children. In that respect, it is worth noting that the FDA document states that Al accumulation at levels associated with central nervous system and bone toxicity may occur at even lower rates of exposure [112]. Thus, a baby weighing ∼3 kg (6.6 pounds) at birth, receives a potentially toxic dose of Al that is 17–30 times greater than the best currently available estimate of 5 μg Al/kg/day, and that from a single HepB vaccine (Table 6). At their 3rd regularly scheduled vaccination appointment, babies weighing ∼5.5 kg at two months (12 pounds), receive 45 to 50 times more Al than what is considered safe by the FDA (Table 6). The long-term consequences of such an aggressive vaccination policy have not been adequately investigated, although it is interesting to note that since the dramatic increase in the number of vaccinations deemed to be required prior to school entry (from 10 in the late 70s to 32 in 2010, 18 of which contain Al adjuvants; Table 6), the prevalence of neurological disorders in children in developed countries has increased by 2000–3000% (from less than 5 per 10,000 [113] to 110–157 per 10,000 [114, 115]). What those who are pro-vaccination assert is that vaccines contain similar amounts of Al to those found in infant formulas [116]. What they fail to stress is that unlike dietary Al of which only ∼0.25% is absorbed into systemic circulation (Table 3), Al from vaccines is absorbed at nearly 100% efficiency [117, 118]. Moreover, the sizes of most antigen-Al complexes (24–69 kDa [119, 120]), are higher than the molecular weight cut-off of the glomerulus of the kidney (∼18 kDa [121]), which would preclude efficient excretion of Al adjuvants. Thus, vaccine-derived Al would have a much greater potential to induce neurological damage than that obtained through diet. It is true that vaccines are not administered on a daily basis; however, they are administered frequently during the most critical period of brain development (Table 6) [38, 111, 122]. Further concern about neurotoxicity risks from Al vaccine adjuvants is warranted by the fact that even adults may be susceptible to adverse effects from these compounds [123–128]. In addition, injection of Al hydroxide in amounts relevant to human vaccine exposure, leads to motor neuron death, increase in brain inflammatory markers, impairments in motor function, and decrements in spatial memory in young outbred CD-1 male mice [87, 129].

Table 5
Dietary Al intake in children. Data compiled from ATSDR [38]

Age	Daily Al intake (mg/day)	Daily Al intake/kg bw (mg/kg/day)	Weekly Al intake/kg bw (mg/kg/day)	÷ PTWI (1 mg/kg/bw)	Major Al food sources
0–3 months	1.5	0.05	3.5	3.5†	Soy-based formula (2.5 mg Al/l) (3 × 200 mL/day)
0–3 months	0.09	0.03	0.21	0.21	Milk-based formula (0.15 mg Al/l) (3 × 200 mL/day)
0–3 months	0.006	0.002	0.014	0.014	Mother's milk (0.01 mg Al/l) (3 × 200 mL/day)
6–11 months	0.7	0.10	0.7	0.7	Soy-based formula, American processed cheese, yellow cake with icing, green beans, strained, pancakes
2 years	4.6	0.35	2.45	2.45†	Cornbread, American processed cheese, yellow cake with icing, fish sticks, pancakes, tortillas, muffins, taco, tea
6 years	6.5	0.30	2.1	2.1†	American processed cheese, yellow cake with icing, pancakes, fish sticks, cornbread, tortillas, taco, muffins, hamburger
10 years	6.8	0.11	0.77	0.77	American processed cheese, cornbread, pancakes, tortillas, yellow cake with icing, fish sticks, taco, muffins, chocolate cake
14–16 years (females)	7.7	0.15	1.05	1.05	American processed cheese, yellow cake with icing, cornbread, taco, pancakes, tortillas, muffins, cheeseburger, tea, fish sticks
14–16 years (males)	11.5	0.18	1.26	1.26†	Cornbread, American processed cheese, pancakes, yellow cake with icing, taco, tortillas, cheeseburger, tea, hamburger, fish sticks

bw – body weight.
† Age groups consuming over the PTWI limit for Al.

Table 6
Al administered to children under the current USA vaccination program [316]. Children from 2–18 months of age who regularly receive multiple vaccinations may exceed current FDA safety limits for Al exposure from parenteral sources (5 μg Al/kg/day [112]) by a factor of 50. Note that these FDA guidelines would be applicable to vaccination since all Al injected from a vaccine would eventually be absorbed into systemic circulation [118]. By 2 and 6 years of age, children receive a total of 5.2–5.9 mg Al and 5.8–6.5 mg Al respectively. HepB-Hepatitis B, RV-Rotavirus, DTP-Diphteria, Tetanus, Pertussis, Hib-Haemophilus influenza type b, PCV-Pneumococcal, IPV-Inactivated Poliovirus, MMR-Measles, Mumps, Rubella, Var-Varicella, HepA-Hepatitis A. Table source: Centers for Disease Control and Prevention (CDC) [316]. Al content in vaccines according to Offit and Jew [116]

Al/dose (mg)↓	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
0.25–0.5	HepB		HepB		HepB						
–			RV	RV	RV						
0.625			DTP	DTP	DTP		DTP				DTP
0.225			Hib	Hib	Hib		Hib				
0.125			PCV	PCV	PCV		PCV				
–			IPV	IPV	IPV						IPV
–							MMR				MMR
–							Var				Var
0.25							HepA		HepA		
–					If			If			If
Al /visit (mg) →	0.25–0.50		1.225–1.475	0.975	1.225–1.475		1.125		0.25		0.625

Regarding other sources of Al exposure in children, according to ATSDR [38], ∼50% of them over the age of 6 months consume more than their PTWI limit for Al, while the remaining 50% are within the upper range (Table 5). Two-year olds consume almost three times their PTWI limit (Table 5), while infants (0–3 months)

fed exclusively with certain soy-based formulas may ingest as much as 1.5 mg Al/day, which is ~250 times the amount they would get from mother's milk and almost three and a half times over their PTWI (Table 5). Out of all infant formulas, highest levels of Al are found in highly processed soy formulas (up to 2.5 mg Al/L), and lowest in products that require no or minimal processing and have few additives, such as human milk (unless the mother consumes a high level of Al additives) and bottled glucose water (<0.05 mg Al/L; Table 4). Al additives are also widely used as preservatives, emulsifiers, leavening, anticaking, and coloring agents [38, 72, 88–91, 93, 94, 97, 98, 130]. Among the most common are: 1) basic sodium Al phosphates (SALPs), emulsifying agents in cheese, and 2) acidic SALPs (which react with sodium bicarbonate to cause a leavening action), used in commercial baking powders, biscuit, pancake, waffle, cake, doughnut, muffin, and self-rising flour mixes [88, 89, 97, 98, 130]. A single serving of a ready-to-eat pancake may yield 4 times the Al PTWI (180 mg; Table 4), while a typical serving of processed cheese (28 g) may provide ~11.5–40 mg of dietary Al (1/7 – >1/2 the PTWI; Table 4). It is worth noting that the same processed food items (including soy infant formulas), which contain Al, often also contain potentially excitotoxic amounts of monosodium glutamate (MSG) [131, 132]. Glutamate significantly enhances Al transport across the BBB and accumulation in AD-susceptible regions (Fig. 4) [133–135]. It may also increase Al absorption from the GI tract [39, 136]). Conversely, Al potentiates glutamate excitotoxic effects *in vivo* [135] in cultured hippocampal pyramidal neurons [50] and in primary neuronal cultures (Table 1) [137]. Notably, neuronal lesions resulting from synchronistic application of Al and glutamate show mitochondrial abnormalities which are characteristic for early excitotoxic events (swelling and disruption of the mitochondria and microvacuolization of the perikaryal cytoplasm) [50].

As early as 1911, William Gies expressed concerns about the use of Al in baking powders [98]. Based on seven years of research on the effects of Al salts in animals and humans, Gies concluded that Al should be excluded from food in the interest of conservation of the most valuable natural resource: human health [98]. More recently, Rogers and Simon [91] who conducted the sole preliminary study to determine whether dietary Al intake differs in individuals with and without AD (and found that AD subjects consumed significantly more of the highest SALP-containing food category, $p = 0.025$), noted: "*Current dietary patterns in the USA are akin to a grand-scale experiment whereby some individuals are consuming large quantities of aluminum while others are not, the long term effects of which have not been investigated. It is important to determine whether William Gies was correct in his admonitions*". Interestingly, the 357 page ATSDR report [38] states that "*Oral exposure to alu-*

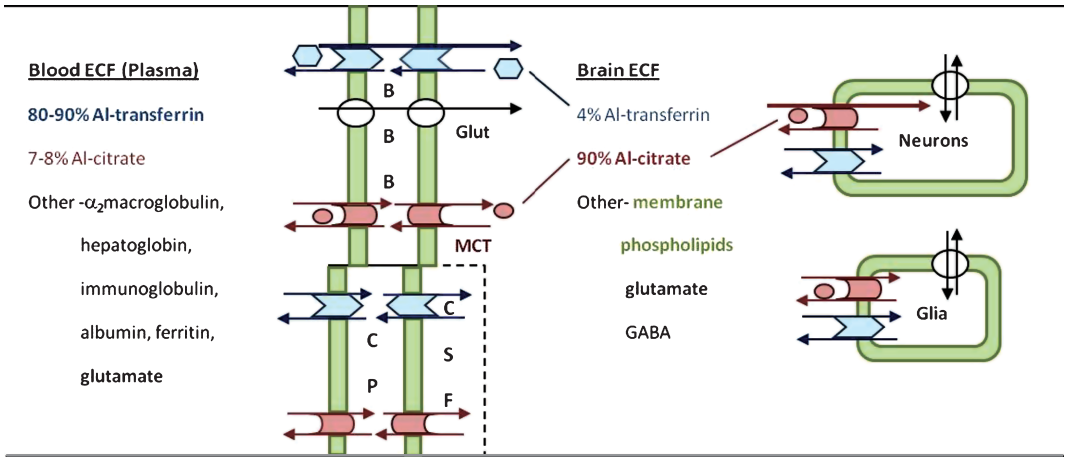

Fig. 4. Major routes of Al transport in and out of the brain: from the blood, Al enters the brain ECF primarily through the BBB via transferrin-mediated uptake. Al influx from the brain ECF to the cellular compartments is mediated by transferrin-dependent and independent mechanisms. Neurons and glia compete for Al uptake from the brain ECF, however, long-lived terminally differentiated neurons tend to accumulate more Al over time. Some Al in the brain is rapidly effluxed as Al-citrate by the MCT-transporter. A significant portion of Al is retained in the cellular compartments (nucleus, ER, bound to ATP or membrane phospholipids). BBB-blood brain barrier, CP-choroid plexus, CSF-cerebrospinal fluid, ECF-extracellular fluid, MCT-monocarboxylate transporter, Glut-glutamate transporter. The dashed line represents the absence of a membrane barrier between the CSF and brain ECF (adapted from Yokel et al. [68]).

minum is usually not harmful", although it recognizes that the neurological effects of such exposure have not been "*adequately investigated in healthy humans*". The report further notes that "*There is a rather extensive database on the oral toxicity of aluminum in animals. These studies clearly identify the nervous system as the most sensitive target of aluminum toxicity*" [38].

The data presented by the ATSDR in relation to Al toxicity following dermal and inhalation exposures in humans is equally scant. The report states that "*Limited information is available regarding the distribution of aluminum following inhalation exposure in humans or animals...No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, ocular, body weight, or metabolic effects in humans or animals after dermal exposure to various forms of aluminum....No studies were located regarding immunological/lymphoreticular effects in humans after intermediate or chronic-duration dermal exposure to various forms of aluminum....No studies were located regarding neurological effects in humans after acute- or intermediate-duration dermal exposure to various forms of aluminum*" [38]. The ATSDR then makes a claim that "*Aluminum compounds are widely used in antiperspirants without harmful effects to the skin or other organs*" [38]. The study which the ATSDR uses to back their conclusion on the safety of antiperspirant use dates back to 1974 [138], even though there are several more recent reports which implicate antiperspirant use with the increased risk of Al-related diseases, including AD [92, 139–141]. Similarly, in response to concerns raised by citizens in regards to the safety of Al-based antiperspirants, the FDA asserts that it "*has no data showing that products containing up to 35 percent aluminum chlorhydrates or aluminum zirconium chlorhydrates increase aluminum absorption and is not revising the monograph to provide for powder roll-on dosage forms containing up to 35 percent antiperspirant active ingredient, without additional safety data being provided*" and that "*the majority of researchers investigating the [cause or origin] of Alzheimer's disease would consider current evidence insufficient to link aluminum to Alzheimer's disease. . .current scientific information does not support the need to reclassify the safety of aluminum-containing antiperspirants*" [142]. A similar view is held by the Alzheimer's Society Canada: "*Most researchers no longer regard aluminum as a risk factor for Alzheimer's disease...At this point, there is no convincing evidence that aluminum increases a person's risk of developing Alzheimer's disease*" [143]. In contrast to such statements, there is solid evidence implicating even less common routes of Al exposure, such as inhalation, in preclinical cognitive and behavioral disorders which might prelude AD [144, 145].

MECHANISMS OF ALUMINUM TOXICITY

Physical and chemical properties: aluminum's toxic mimicry

Much like mercury, and unlike iron, copper, zinc, and manganese, Al has no biological role and is unquestionably a neurotoxin [32, 38, 39, 146]. A small ionic radius and high charge are main properties by which Al exerts its neurotoxic activity. The Al ion (0.054 nm) is roughly the same size as the ferric ion (0.065 nm) and much smaller than magnesium (0.072 nm) and calcium ions (0.100 nm). In biological systems, Al can effectively replace these essential biometals in many enzymatic reactions [39, 147–151]. For example, Al binds the extracellular-iron carrier transferrin [19, 146, 152] which in turn, may facilitate its transport across the brain barriers (Fig. 4). Furthermore, due to its greater affinity for anionic groups, Al potently interferes with reactions that depend on reversible dissociation. Processes involving rapid Ca^{2+} exchange are inhibited by Al substitution [6, 39, 150, 151]. Similarly, at nanomolar concentrations, Al inhibits many Mg^{2+} and ATP-dependent enzymes, including: tubulin GTPase [149], Na^+ K^+ ATPase [153], hexokinase [146, 154], RNA polymerase [155–157], choline acetyltransferase [158–160], ferroxidase (ceruloplasmin [161]), calmodulin-dependent ATPase [6, 148, 150], as it binds ATP in a complex that is several orders of magnitude more stable than that with magnesium (the association constant for Al^{3+} is 10^7 times that of Mg^{2+} [149]).

Al also binds other nucleotides (GTP and CTP) [162] as well as phosphate headgroups of lipid moieties in membrane systems. Apart from altering membrane properties [163], it has the potential to interfere with any reaction that requires phosphoryl transfer and ATP/GTP hydrolysis [6, 39, 147]. As mentioned previously, Al in solution readily associates with fluoride to form highly toxic fluoroaluminate complexes, which are well known to interfere with the activity of G-proteins and calcium homeostasis [39, 77–81]. Given the ubiquity of enzymatic systems and signaling cascades that depend on GPCR signaling, phosphorylation, ATP, GTP, calcium, magnesium, and iron, the spectrum of physiological processes that can be

adversely affected by Al is extremely vast. In spite of this, in the absence of chronic renal failure, the toxic effects of Al (especially at low doses) appear to be primarily manifested in the brain (Table 1) [2, 6, 18, 19, 38, 47, 48, 50, 63, 70, 87, 107, 133, 146, 163–170], although in vulnerable populations such as infants, prolonged exposure at both high and low doses of Al may also lead to metabolic bone disease [171, 172]. Notably, Al neurotoxicity appears to be compartmentalized as highly sensitive imaging techniques, as well as methods for quantifying focal accumulations of Al, repeatedly show that Al associates with specific brain regions and cellular compartments [2, 41–44, 46–48, 59, 165, 173, 174]. That Al is a neurotoxin is beyond debate, what appears to be or may be debatable is whether it contributes to AD.

Regulation of body aluminum burden: neurotoxicity increases with aging

In the human body Al burden is partitioned at four levels: GI tract, blood-kidneys, brain barriers, and brain extracellular fluid (ECF) [6, 27, 39, 68, 175, 176]. While the efficiency of absorption from the GI tract and removal by the kidneys determines the amount of Al in the blood, regulation at the brain barrier/brain ECF levels determines where in the brain Al is distributed [6]. Systemic regulation of Al is far more complex than initially thought as there are numerous factors that affect Al partitioning at all four levels (Table 3 – see footnote; Fig. 4) [6, 38, 39, 88, 93, 109, 135, 136, 177, 178]. The regulation of the Al burden by the brain is geared towards maintaining optimal neuronal function [6]. There are specific transport mechanisms which ensure active and dynamic distribution of the Al burden in the brain and this partially mitigates its neurotoxic effects [6, 63, 68, 175]. These observations indicate that the earlier animal models of neurofibrillary degeneration (based on intracerebral injection of Al), may not be adequate in assessing the significance of bioavailable Al in the etiology of AD. Likewise, dialysis dementia is not representative of a truly chronic exposure to dietary ingested Al-the chief risk for the majority of people, as the GI barrier is bypassed by intravenous dialysate delivery. Furthermore, patients with disabled urinary clearance undergoing chronic treatment with Al-contaminated dialysate, accumulate Al in tissues other than brain (primarily bone and red blood cells; Table 2) [56, 179, 180]. In contrast, in healthy people only a minor fraction of Al is absorbed from the GI tract (<1%) [33, 39, 88, 93], which is then in large proportion removed by the kidneys. Hence, symptoms of Al intoxication only become apparent when kidney function is impaired, which occurs normally during aging as humans lose up to 50% of their glomeruli between 40 and 85 years of age [181]. Kidneys are a major route by which metals are excreted from the blood, and their essential role in eliminating excess Al is emphasized by *in vivo* observations which show that concurrent with neurodegeneration, Al intoxication is often accompanied by elevated Al kidney burden, glomerular distortions, and renal failure [82].

Thus, when urinary clearance is impaired, the risk of Al neurotoxicity significantly increases as it increases the Al brain burden. This implies that a strong predisposition for gradual accumulation of metabolic errors consequent to Al toxicity, is somewhat inherent to the aging process and explains how a life-long exposure to low doses of Al could lead to Al accumulation in neural cells and instigate a progressive cascade of subtle neuropathological events that culminate in AD. This contention is supported by the late age of onset of clinical symptoms (>65 years) and relatively slow progression of idiopathic AD (average duration of illness is 10 years; Table 2), as well as experimental evidence: 1) older persons have typically higher brain Al content than younger ones [41], and subjects with AD have an even higher content than non-demented age-matched controls (Table 2), 2) lower levels of serum Al than those routinely reported in dialysis patients are known to produce cognitive impairments associated with AD [169]. Performance in behavioral tests correlates with serum Al levels in elderly subjects and elevated Al is associated with impaired visuo-motor coordination, poor long-term memory and increased sensitivity to flicker. Remarkably, the same effects are seen in rats chronically fed with Al [169]. 3) Analysis of brain tissue from AD patients shows a stage-specific accumulation of Al in hippocampal neurons [47], 4) the studies of Walton [2, 48, 70], elegantly demonstrate that in rats, even at low doses, chronically administered dietary Al preferentially accumulates in AD-susceptible brain compartments, at levels sufficient to up-regulate AβPP mRNA and protein expression.

The implication of these observations is that incremental acquisition of small amounts of Al (as through dietary intake), favors its selective accumulation in brain tissues. The association between distribution of brain Al and AD pathology likely implicates specific transport mechanisms, both circulatory and at the level of brain barriers/brain ECF. Less likely, however, remains the possibility that such compartmentalized

distribution reflects the impact of transport by non-Al specific processes.

Aluminum toxicokinetics across the brain barriers: more than just diffusion

Normal brain function is critically reliant on the efficacy of brain barriers to maintain the delicate neurochemical balance between neurons and their synaptic connections [111]. Both, the BBB and the choroid plexus (CP), play major roles in maintaining this balance by regulating the exchange of substances between the blood ECF (plasma) and brain ECF (Fig. 4), and thus any agent that can alter membrane properties has a potential to initiate neurotoxic events. Alteration in brain barrier permeability is not a prerequisite for Al entry into the brain, as Al sequesters a myriad different transport mechanisms to actively traverse membrane systems, including receptor mediated endocytosis and carrier-mediated transports (Fig. 4). The surface area of the BBB capillaries in humans is $\sim$12 m^2, which is $\sim$10,000-fold that of the choroid plexus (10 cm^2) and experimental evidence strongly implies that plasma Al gains entrance to the brain ECF via the BBB route, rather than through the CP (Fig. 4) [68]. Furthermore, the kinetics of brain Al transport unequivocally points to a carrier-mediated process and not passive diffusion [27, 63, 68, 175]. Once in the brain ECF, Al will either bind to polar headgroups of membrane phospholipids, or enter intracellular pools, most probably via transferrin uptake, monocarboxylate transporter (MCT) – and/or organic anion transporter-mediated mechanisms [6, 27, 68, 152, 175]. Endoplasmic reticulum (ER), nuclear chromatin, hyperphosphorylated tau, and ATP are believed to be the major binding targets of intracellular Al [6, 174, 182–184]. Repeated chelation therapy with DFO in ^{26}Al-treated rats shows that some Al persists in the brain for a long time (half-life of brain ^{26}Al was estimated to be 150 and 55 days in the control and DFO-treated group respectively) [68]. These data indicate that Al is tightly bound to intracellular pools and are consistent with frequent observations of perinuclear and nuclear foci of Al in AD brains [10, 42, 47, 59, 182, 185].

Pyramidal neurons are a population of brain cells that are particularly susceptible to Al accumulation and toxicity [2, 43, 47, 50, 70]. These are also the largest cells in the brain and one of the most vulnerable cell populations in AD [1, 10, 43, 186, 187]. Cognitive abilities as well as psychomotor control are intimately associated with function of pyramidal cells [188, 189]. It is well known that brain tissue has a limited proliferative capacity and as such, an intrinsic tendency for accumulating metals [19, 146, 152, 190]. Toxins are diluted in undifferentiated cells undergoing mitosis. However, because pyramidal neurons are terminally differentiated, the Al transported into these cells will tend to accumulate over time. When accumulation of metabolic errors at susceptible foci exceeds a certain threshold, as a result of persistent latent Al toxicity, clinical symptoms will become apparent. Consistent with this hypothesis, abnormally high levels of Al are routinely found in AD brains, up to fourfold the level of healthy controls (Table 2) and sensitive quantifying techniques demonstrate that perikarya of pyramidal cells of the hippocampus and entorhinal cortex are foci where Al accumulation is most pronounced, while interneurons are spared [2, 43, 47, 50].

It is quite clear that Al partitioning within the brain is highly complex and dynamic (Fig. 4). There are three principal sources of bioavailable brain Al: extracellular, membrane-bound, and intracellular. There is also a further sub-partitioning among these sources. Unlike the former two, the intracellular Al pool does not appear to be readily mobilized as the kinetic control at the level of terminally differentiated neurons favors its accumulation (Fig. 4). This provides the basis for a region-specific accumulation of Al, in a manner that highly implicates its involvement in AD.

Fate of dietary aluminum: implications for dysregulation of iron homeostasis and oxidative damage

Al absorbed from the GI tract either becomes rapidly bound to various high-molecular-weight carrier proteins (including the iron-specific carriers transferrin and ferritin as well as α_2-macroglobulin, immunoglobulin, hepatoglobin, and albumin) [19, 27, 68, 191–193] or by low-molecular ligands such as citrate (Fig. 4) [27, 175]. Experimental evidence has suggested that at equilibrium, 80–90% of total Al in the plasma is carried by transferrin [39, 68, 192], the chief iron transport protein in vertebrates [19, 25, 152]. Although the relative proportions of different Al complexes may be different in non-equilibrium [194], it is the high molecular weight-bound fraction of plasma Al (such as transferrin-Al) that is perhaps more biologically relevant, since it is refractory to excretion by the kidneys [38, 93]. Transferrin has a similarly high affinity for Al^{3+} ions as for Fe^{3+} ions [152] and typically, even under conditions of iron overload, only 30% of transferrin is occupied by iron [19]. This leaves a potentially high fraction of free transferrin avail-

able to Al and other metal ions which have been shown to bind transferrin (zinc, gallium, manganese) [152]. The cellular intake of transferrin-bound iron occurs via transferin receptor (TfR)-mediated endocytosis of the TfR-transferrin (iron) complexes [27, 68, 152, 195–197]. Several reports indicate that density and binding to TfRs is decreased in AD. Morris et al. [196] report a reduction in binding to TfRs in pyramidal cell layers of the hippocampus in AD brains, which led them to conclude that TfR-mediated Al uptake is not a major contributor to AD. However, such localized loss of TfR-mediated endocytosis would not significantly affect hippocampal Al uptake since it is estimated that only ~4% of Al within the brain ECF pool is bound to transferrin and ~90% is bound to citrate, a vehicle for the MCT transporter (Fig. 4) [68]. Furthermore, Al is known to use TfR-independent mechanisms to gain access to brain compartments from the brain ECF and the most likely candidate for this process is citrate, the major Al carrier in the brain ECF (Fig. 4) [27, 68, 175]. Most notably, recent research evidence shows that Al-transferrin complexes are not bound by the TfR [198–200] because of an incomplete open/closed form which precludes them from forming specific ionic inter-residual interactions, such as those formed by iron-transferrin and the TfR [198]. This implies that Al-transferrin transfer from the blood stream to cytoplasm may not follow the classical iron-TfR acquisition pathway. Nonetheless, cellular uptake of Al-transferrin complexes has been observed in different cell lines [201–204] indicating that such complexes may be utilizing a yet unknown mechanism by which they circumvent the incompatibility with the TfR to gain access to the intracellular milieu. Apart from transferrin, Al may also bind to the chief iron storage protein ferritin, and according to a study by Fleming and Joshi [205], ferritin-bound Al isolated from AD brains is 6-fold higher than that from age-matched controls. Nonetheless, some investigators have reported relatively little Al in ferritin deposits [206, 207], suggesting that less Al is sequestered and more is freely available to cause damage in cells [206].

Free iron is thought to be a principal mediator of oxidation in cellular systems due to its ability to generate highly reactive oxidative species (ROS) via Fenton chemistry [19, 26, 137, 208–210]. Unlike iron, Al is redox inert and its ability to induce oxidative damage is related to a synergistic action that involves iron [209, 211, 212]. Experimental evidence suggests that senile amyloid plaques can act as sinks for free metals, both redox active (iron and copper) and redox inactive (zinc and Al) [213]. In addition, it has been shown that $A\beta_{42}$ can influence the Fenton chemistry through aggregation state-specific binding of both ferrous iron, Fe(II) and ferric iron, Fe(III). According to Khan et al. [213], the net result of these interactions was a delayed precipitation of redox-inactive iron (III) hydroxide, $Fe(OH)_3$, such that Fe(II)/Fe(III) were cycled in redox-active forms over a substantially longer time period than if peptide had been absent from preparations. Further aggregation state-specific binding of both Fe(II) and Fe(III) determined critical equilibria involved in the formation of hydrogen peroxide via the superoxide radical anion in favor of maintaining Fe(II) in solution [213]. The additional presence of Al, copper and zinc influenced both the aggregation state of $A\beta_{42}$, and therefore its binding of Fe(II) and Fe(III), as well as the redox chemistry, most specifically through direct interactions with the superoxide radical anion which is heavily implicated in ROS mediated neurotoxicity [213]. Finally, it was demonstrated that the addition of pathophysiologically significant concentration of Al exacerbated superoxide radical anion -induced toxicity in the presence of $A\beta_{42}$ while both copper and zinc, mitigated against oxidative damage but only providing that Al was absent [213].

In conclusion, it is evident that by hijacking several cellular transport mechanisms, Al gains direct access to brain tissue, and that not all areas of the brain are equally capable of removing the burgeoning Al burden. Thus, long-term, the overt manifestations of Al neurotoxicity may not be determined by the rate of Al influx as much as Al efflux. Taken together, these observations nullify the arguments that Al cannot enter the brain actively and/or in sufficient amounts to cause damage, and that cellular transport routes are not effectively exploited by Al to the extent in which it could have an impact on AD. Because of its high neurotoxic potential, the factor that is of particular relevance in regards to the risk for AD, is that small amounts of Al can access the brain continually, to a point at which neurotoxicity occurs. As documented (Tables 3–5), this criterion is satisfied through dietary Al intake.

BRAIN COMPARTMENTALIZATION: BASIS FOR ALUMINUM'S SELECTIVE NEUROTOXICITY IN AD

Interference with glucose metabolism and damaging effects on the myelin sheath

What makes the brain in general and certain brain areas specifically more susceptible to Al toxicity? In answering these questions, it should be emphasized

that brain is a highly compartmentalized organ, both at systemic, tissue, as well as cellular levels. On a systemic level, the brain has intrinsically high glucose and oxygen requirements [19, 214, 215], high surface area of biological membranes (especially vascular endothelium) [68], high tubulin content [20], high phospholipid content, and a low concentration of antioxidants, compared with other organs [212, 215, 216]. For example, although an adult human brain only weighs ~1.5 kg, it consumes 20% of total body oxygen and 120 g of glucose/day, compared to 190 g for the whole body [19]. Furthermore, the utilization of glucose varies in response to different stimuli and among brain compartments [217]. More than 80% of brain glucose is used in the glycolytic pathway that requires ATP/magnesium-dependent activity of hexokinase, while the rest is metabolized by the glucose-6-phosphate dehydrogenase (G6PD)-dependent shunt pathway [19].

Experimental evidence has shown that Al interferes with glucose metabolism by inhibiting both hexokinase and G6PD [19, 146, 154]. The latter is of special significance since the shunt pathway is primarily utilized by myelinated neurons and its activity is dependent on the degree of myelination [218]. Furthermore, as shown by Verstraeten et al. [212], Al (due to its lipophilic nature), binds avidly to membrane phospholipids and by inducing changes in phospholipid rheology (Table 1), promotes lipid peroxidation (LPO). Consequently, myelin (due to its high lipid to protein ratio, 70 : 30 and relatively low ubiquinol content, as opposed to synaptic membranes, 30 : 70), is the preferred target of Al-mediated oxidative damage both *in vitro* and *in vivo* [212]. Moreover, chronic oral exposure to Al in rats markedly reduces the content of specific classes of membrane phospholipids in the brain myelin sheath [216]. Specifically, Al-fed rats show a 70% decrease in acidic phosphatidylinositol (PI), phosphatidylserine (PS), and phosphatidic acid (PA), an effect which is expected to alter charge distribution and insulation properties of the myelin membrane [216]. Alterations of the myelin sheath may lead to dysfunctions in memory and cognition while a marked reduction of the brain PI content is likely to cause deficiencies in inositol phosphate (IP) signaling (Fig. 2). Both of these effects have been observed in Al-treated animals [63, 150, 167, 219, 220] and are also common to AD [3–5, 8, 22, 23].

It is interesting to note that the highest myelin content is associated with pyramidal cells. Studies suggest that axon collaterals of pyramidal neurons contribute most to the total myelin brain content, and that non-pyramidal neurons and afferent fibers play a minor role [221]. Moreover, it has been demonstrated that a progressive loss of myelin in the human nervous system occurs after the age of 30 years and that people suffering from presenile and senile dementia have a reduced myelin content compared to healthy people [222]. It is noteworthy that, with advancing age, there is a concomitant loss of myelin content along with the deterioration of kidney function [181]. This observation reinforces the notion that a predisposing susceptibility to Al neurotoxicity is inherently and incrementally acquired during aging, thus exacerbating the risk for idiopathic AD.

As shown by Walton, cognitively impaired Al-fed rats develop substantial hippocampal and cortical lesions (related to NFTs), consisting of Al-loaded pyramidal neurons [2, 48, 70]. These cells also show significant morphological abnormalities, displaying swollen neurites with varicosities along their length, and myelin matter which is strongly immunoreactive for AβPP [2, 70]. Finally, the progressive structural changes reported to occur during aging in cortical pyramidal neurons remarkably resemble those induced by chronic dietary Al intake and include a reduction in neurite number, length, and branching and ultimately, the appearance of varicose deformities [222]. It is tempting to speculate that these age-related neuronal aberrations may be partly due to cumulative age-dependent effects of Al toxicity.

Compartmentalization by the cytoskeleton: how aluminum triggers NFTs

The neuron is a highly cross-linked compartment with extensive transport and communication networks which are imparted by the cytoskeleton. MTs, neurofilaments (NFs), and MAPs, are essential cytoskeletal components that sustain neuronal function [20, 223]. Since breached integrity of the cytoskeleton is detrimental to neuronal function, any significant interference with its structural components can result in neuronal de-differentiation or possibly death. The brain's cytoskeletal system is somewhat unique as it achieves compartmentalization at tissue, cellular and subcellular levels. The brain has a far higher tubulin content than other tissues [20], which may be related to its intrinsically high metabolic activity and greater distance requirements for cellular transport. There are several tubulin isoforms and their distribution varies between different brain and cellular compartments [20]. NFs localize to axons and dendrites and primarily function in stabilizing the axonal cytoskeleton and

promoting neurite outgrowth [223, 224]. Adding to the complexity of the cytoskeletal lattice are the MAPs, which promote the assembly of tubulin into MT polymers [20, 223]. Furthermore, like tubulins and NFs, MAPs also tend to be compartmentalized within neurons [20]. Notably, both tau and NFs contain multiple phosphorylation sites and are subjected to regulation by various kinases and phosphatases [1, 225–227]. It is proposed that the functional compartmentalization that characterizes brain cells is enabled by a distinctive localization of cytoskeletal components.

There are numerous components of the MT system which are susceptible to Al (Table 1). One major mechanism by which Al preferentially impairs pyramidal neurons is by disabling their capacity for MT assembly [2, 10, 70]. This would cause disruption of axoplasmic and dendritic transports, neurite damage, and eventually, cell death [186]. Consistent with this, Al accumulation in pyramidal cells from AD brains is associated with depletion of MTs and abundance of NFTs that contain Al [2]. Accordingly, rats chronically exposed to low dietary Al show cognitive impairment concomitant with pyramidal cell Al accumulation and microtubule depletion, shriveling neurites and synapse loss [2, 70]. Likewise, Al-induced neurofibrillary degeneration in rabbits selectively affects cortical pyramidal neurons while sparing interneurons [43].

Oxidative stress and lipid peroxidation

Oxidative damage is thought to be an early event in AD [17, 21, 228, 229] and Al is a known pro-oxidant *in vivo* (Table 1) [164, 166, 230–232]. Al potentiates oxidative damage by multiple mechanisms: it inhibits the key free-radical scavenging enzymes superoxide dismutase (SOD) and catalase [164], increases LPO [212, 231], and modulates the induction of neuronal nitric oxide synthase [232]. High metabolic activity and low free radical buffering capacity, coupled with 400 miles of brain capillaries (and associated membrane phospholipids) within the BBB [68], make the human brain a prime target for Al-induced oxidative damage. Accordingly, oxidative stress in the brain is primarily manifested as LPO, due to its exceptionally high content of polyunsaturated fatty acids (PUFAs, constituents of membrane phospholipids), that are particularly vulnerable to oxidation [21, 229]. Isoprostanes (iPs) are chemically stable isomers of prostaglandins (formed by peroxidation of PUFAs) and specific and sensitive markers of *in vivo* LPO [233–235]. Studies show that levels of a major iP marker 8,12-*iso*-iP$F_{2\alpha}$-VI are increased postmortem in AD-susceptible brain compartments [235] as well as in the urine, plasma, and cerebrospinal fluid (CSF) of patients with a clinical diagnosis of AD [234] where 8,12-*iso*-iP$F_{2\alpha}$-VI levels correlated with disease severity. Remarkably, these observations were experimentally reproduced in a mouse model of AD-like amyloidosis (Tg2576), in which mice overexpress a double mutant human AβPP transgene. In Tg2576 mice, chronically administered dietary Al increased 8,12-*iso*-iP$F_{2\alpha}$-VI levels in the hippocampus and neocortex and concomitantly, also increased Aβ levels and stimulated plaque deposition [231]. Notably, none of these pathogenic changes were observed in Tg2675 mice fed a regular chow diet. Moreover, Al-induced increases in 8,12-*iso*-iP$F_{2\alpha}$-VI levels and amyloid plaque burden in the hippocampus and neocortex were directly correlated and almost completely reversed by supplementation with antioxidant vitamin E. Furthermore, early in the course of treatment, plasma and urine 8,12-*iso*-iP$F_{2\alpha}$-VI levels also increased in Al-fed mice, but they were reduced in mice supplemented with vitamin E [231]. These results provide compelling *in vivo* evidence that dietary Al can drive and accelerate the amyloid cascade by potentiating LPO and oxidative stress. They are also in concordance with emerging data from prior experiments in Tg2576 [21], as well as studies of AD patients, which indicate that increased levels of 8,12-*iso*-iP$F_{2\alpha}$-VI in blood or urine appear to precede the onset of AD, and that LPO is central to AD [234]. Similar effects of Al on oxidative stress were observed in rats (both adult and pups), where chronically administered Al (by daily oral gavage) significantly increased LPO and decreased the activity of two key antioxidant enzymes, SOD and catalase in specific brain regions [164].

Effects on chromatin structure and transcription

The nucleus is another prime target for Al toxicity due to its high anionic microenvironment (Table 1) [155, 236]. Consistently, focal accumulation of Al in neuronal nuclei has been widely documented and recognized as a distinguishing feature in AD [42, 47, 59, 156, 174, 185]. Al binds to phosphonucleotides and alters DNA interaction with nucleoproteins, transcription factors and RNA polymerase. The effects of nuclear Al have been extensively studied and are accordingly best summarized by Lukiw et al. "*The presence of aluminum is an impediment to normal brain gene function*" [155]. At nanomolar concentrations, Al inhibits brain-specific gene transcription from selected AT-rich promoters of human neocortical

genes [155]. Al repressive action on gene transcription is linked to its ability to: 1) decrease the access of transcriptional machinery to initiation sites on DNA template by enhancing chromatin condensation [174, 182–185], 2) interfere with ATP-hydrolysis-powered separation of DNA strands either indirectly (by binding to phosphonucleotides and increasing the stability and melting temperature of DNA) [155, 236] or directly (by inhibiting the ATPase-dependent action of RNA polymerase) [155]. These effects were experimentally demonstrated at physiologically-relevant Al concentrations (10–100 nm [155, 157]) and at levels that have been reported in AD chromatin fractions [185]. Of particular relevance, highly condensed cortical chromatin fractions and increased linker histone content on dinucleosomes are typical features of both idiopathic and familial AD [185]. Al is well known to promote chromatin compaction by increasing the association of DNA with linker histones $H1^0$ and H1 [174, 182, 184, 185]. Accordingly, compared to aged matched controls, AD subjects show a nine-fold increase in Al content in the dinucleosome fraction containing repressed neuronal genes. Moreover, a highly significant correlation was found between the Al DNA ratio and the degree of chromatin compaction [65, 185].

It is particularly interesting to note that in spite of its overall repressive action, Al can also promote transcription. Based on experimental evidence, it has been suggested that by promoting LPO and oxidative stress, Al activates the ROS-sensitive transcription factors, hypoxia inducible factor-1 (HIF-1) and nuclear factor (NF)-κB and augments specific neuroinflammatory and pro-apoptotic signaling cascades by driving the expression from a subset of HIF-1 and NF-κB – inducible promoters [209, 237]. Out of eight induced genes up-regulated in cultured human neurons by 100 nm Al sulfate (the same compound that is used as a flocculant in water [38, 39]), seven showed expression patterns similar to those observed in AD, including HIF-1/NF-κB-responsive AβPP, interleukin-1β (IL-1β) precursor, NF-κB subunits, cytosolic phospholipase A_2 ($cPLA_2$), cyclooxygenase (COX)-2, and DAXX, a regulatory protein known to induce apoptosis and repress transcription [237]. Both HIF-1 and NF-κB are up-regulated in AD where they fuel the pro-inflammatory cycle which leads to further exacerbation of oxidative stress and inflammation, culminating in neuronal death [16, 155, 209]. The ability to induce HIF-1/NF-κB-dependent up-regulation of AβPP may well be the underpinning mechanism by which Al triggers oxidative stress-mediated amyloidosis in Tg2576 mice [231].

Interference with neurotransmission, G-proteins, and calcium homeostasis

Dysregulation of G-protein mediated signal transduction and calcium homeostasis is central to the etiology of AD and it is thought to precede the amyloid cascade and NFT changes [4, 5, 8, 12, 238]. G-proteins and calcium modulate vital neuronal processes such as neurotransmission, synaptic plasticity, and apoptosis [3, 12, 23, 28]. Al interferes with several components of the two principal G-protein signaling pathways: GPCR-regulated 1) phospholipase C (PLC)/inositol 1,4,5-trisphosphate (IP_3) and 2) adenylate cyclase (AC)/cyclic AMP (cAMP) pathway (Table 1, Fig. 2). Alterations in both of these pathways have been demonstrated in AD brains at numerous levels [3–5, 8, 28, 239]. Explicitly, impaired response to G_q-cholinergic muscarinic receptor agonist-induced PI hydrolysis by PLC, decreased levels and activity of PKC and the loss of IP_3 receptors in the entorhinal cortex and hippocampus correlate with AD-NFT pathology [3–5, 8, 239]. Disruptions in the AC pathway in AD include impairments at the level of G_s-protein stimulation of AC [5], increased cAMP in cerebral microvessels [239] and loss of calcium/calmodulin (CaM) sensitive AC isoforms [5]. Overall, G-protein levels are largely preserved in AD, indicating a functional deficit [4, 5, 8].

Al action on G-proteins has been shown to be highly specific. While Al inhibits G_q-mediated PI hydrolysis by PLC, it stimulates G_s-mediated cAMP production by AC (Table 1, Fig. 2). Most notably, these effects were observed *in vivo* after chronic oral exposure to Al-treated drinking water in weanling and adult rats [167]. In summary, impaired response to agonists at G_q/G_s levels, elevated cAMP, PLC inhibition and IP_3 decrease and impairment of calcium/CaM-dependent enzymes are specific signatures of Al neurotoxicity (Table 1, Fig. 2). These changes perfectly reproduce the hallmark changes observed in AD [3–5, 8, 28, 239]. Similarly, the neurotoxic effects of Al mimic cholinergic dysfunction, another hallmark of AD, in a manner that highly implicates its central role in the pathogenesis of this disease (Table 1). Acetylcholine (ACh) release from cholinergic neurons alters the excitability of hippocampal pyramidal neurons [150]. By interfering with G-proteins and altering calcium homeostasis, Al toxicity causes reductions in neuronal excitability, impairs neurotransmission and progressively leads to memory and learning deficits. Furthermore, by inhibiting agonist-mediated stimulation of cholinergic muscarinic receptors and disabling the IP_3/PLC signal

transduction pathway, Al may shift AβPP processing towards an increase in production of the neurotoxic Aβ-peptide, at the expense of the neuroprotective α-secretase-derived soluble AβPP (sα –AβPP; Table 1, Figs 1 and 2). This would explain gross abnormalities in neurite morphology, losses of synapses and neurons that are seen to occur concomitantly with AβPP upregulation in Al-fed rats [2, 70, 82, 83]. This is also consistent with the type of damage observed in AD brains [2, 70, 82, 83], given that sα-AβPP function is required for proper neurite outgrowth and branching [240, 241] and to counteract pro-apoptotic signaling and synaptogenesis [241, 242]. It is worth emphasizing that Al may induce amyloidosis by up-regulating AβPP expression, altering AβPP processing and trafficking to increase the production of toxic Aβ species, and promoting their aggregation into fibrillar structural constituents of senile plaques (Table 1, Figs 1 and 2). Thus, it appears that all pathological parameters required for amyloidogenesis are efficiently targeted by Al.

In summary, it is evident that the brain's structural and functional heterogeneity provides a basis for differential susceptibility of specific neuronal populations to Al toxicity. The above observations re-emphasize the hypothesis that Al aggravates the risk of developing age-related dementia of the Alzheimer type, by driving subtle though persistent incremental deterioration of neural functions at a susceptible foci.

CONCLUSIONS

Al is the third most abundant element on earth, widely bioavailable to humans and a definite neurotoxin and AD is the most prevalent neurodegenerative disease at the present age. The hypothesis that Al significantly contributes to AD, more so than any other single factor investigated, is built upon very solid experimental evidence. Al has a direct and active access to the brain where it accumulates in a region-specific manner that highly implicates its involvement in AD. Experimental data clearly shows that all neurophysiological parameters required for AD are efficiently targeted for impairment by Al. The sum of latent neurophysiological alterations which are known to precede overt clinical manifestations of AD and are consistent with Al's neurotoxic properties are: 1) enhanced amyloidosis, 2) neurofibrillary abnormalities, disruption of axonal transport mechanisms, neurite degeneration, and loss of synapses, 3) deficits in neurotransmission (particularly cholinergic) and impairment of G-protein signal transduction cascades, 4) disruption of neuronal energy metabolism and brain metal homeostasis (particularly calcium iron and magnesium), 5) potentiation of oxidative stress and peroxidation of brain membrane lipids, 6) disruption of brain barriers, 7) alterations in chromatin structure and impairment of transcription, and 8) upregulation of stress-related pro-inflammatory and pro-apoptotic pathways. The latter may be of special significance since elevated levels of intrinsic inflammation are associated with neural aging and further exacerbated in several neurodegenerative diseases. In stark contradiction with the abundance of research evidence (Table 1), there appear to be "*several hostile intellectual attitudes*" [14] that reject the possibility that Al toxicity contributes to the growing incidence of AD [243, 244]. Such widely circulated opinions hamper implementation of preventative plans to lessen exposure to Al, which, according to some leading scientists' advice, would be the most sound and cost-effective approach to reduce the growing incidence of Alzheimer's type dementia [32, 33, 91, 98, 100, 245, 246]. Given the great socio-economical impact of AD, immediate steps should be taken to minimize human exposure to Al, the single most avoidable factor that poses a serious risk for developing AD. The failure of government health policy makers to take into account the most recent animal studies [2, 48, 61, 70, 82, 83, 107, 165, 167, 178, 231], as well as epidemiological data [99–105, 108] which clearly relate long-term Al ingestion at levels relevant to human exposure to an increased risk of cognitive impairment and dementia of the Alzheimer-type, leads to human AD cases as a major means for demonstrating the neurotoxic potential of Al. This practice is unacceptable but unfortunately prevalent at the present time: "*Current dietary patterns in the USA are akin to a grand-scale experiment whereby some individuals are consuming large quantities of aluminum while others are not, the long term effects of which have not been investigated*" [91]. It would appear that the practical considerations of warnings given by William Gies are now 100 years overdue "*These studies have convinced me that the use in food of aluminum or any other aluminum compound is a dangerous practice. That the aluminum ion is very toxic is well known. That aluminized food yields soluble aluminum compounds to gastric juice (and stomach contents) has been demonstrated. That such soluble aluminum is in part absorbed and carried to all parts of the body by the blood can no longer be doubted. That the organism can "tolerate" such treatment without suffering harmful consequences has not been shown. It is believed that*

the facts in this paper will give emphasis to my conviction that aluminum should be excluded from food" [98]. The same rationale would apply for Al in skin-care products, antiperspirants, pharmaceuticals, and perhaps significantly in vaccines, at least until independent research is available to demonstrate that these products can be used safely. In particular, Al in adjuvant form carries a risk for long-term brain inflammation, cytotoxicity, and associated neurological complications, and may thus have profound and widespread adverse health consequences. We are long overdue for a comprehensive evaluation of the overall impact of Al on human health. With regards to AD, such an evaluation should include studies designed to elucidate the molecular mechanisms involved in the neurotoxicity caused by chronic Al intake and its association with the metabolism of other compounds such as iron. Special emphasis should be given to Al species which are most relevant to human exposure (e.g., fluoroaluminates, Al hydroxide, Al sulfate). As for the reasons for the current complacency about Al toxicity to humans from bioavailable sources, some on the other side of the issue have noted that: "*Some have argued that I should have been more vocal about the fact that paid consultants for the aluminum industry served as consistent and vocal critics of our findings. I always felt, perhaps naively, that our data were properly collected, honestly and completely reported and were essentially correct. Accordingly, I have felt that the truth would eventually be known and ultimately accepted*" [247]. Food for thought?

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REFERENCES

[1] Thomas P, Fenech M (2007) A review of genome mutation and Alzheimer's disease. *Mutagenesis* **22**, 15-33.

[2] Walton JR (2009) Brain lesions comprised of aluminum-rich cells that lack microtubules may be associated with the cognitive deficit of Alzheimer's disease. *Neurotoxicology* **30**, 1059-1069.

[3] Thathiah A, De Strooper B (2009) G protein-coupled receptors, cholinergic dysfunction, and Abeta toxicity in Alzheimer's disease. *Sci Signal* **2**, re8.

[4] Garcia-Jimenez A, Cowburn RF, Ohm TG, Lasn H, Winblad B, Bogdanovic N, Fastbom J (2002) Loss of stimulatory effect of guanosine triphosphate on [(35)S]GTPgammaS binding correlates with Alzheimer's disease neurofibrillary pathology in entorhinal cortex and CA1 hippocampal subfield. *J Neurosci Res* **67**, 388-398.

[5] Cowburn RF, O'Neill C, Bonkale WL, Ohm TG, Fastbom J (2001) Receptor-G-protein signalling in Alzheimer's disease. *Biochem Soc Symp* **67**, 163-175.

[6] Exley C (1999) A molecular mechanism of aluminium-induced Alzheimer's disease? *J Inorg Biochem* **76**, 133-140.

[7] Davis DG, Schmitt FA, Wekstein DR, Markesbery WR (1999) Alzheimer neuropathologic alterations in aged cognitively normal subjects. *J Neuropathol Exp Neurol* **58**, 376-388.

[8] Greenwood AF, Powers RE, Jope RS (1995) Phosphoinositide hydrolysis, G alpha q, phospholipase C, and protein kinase C in post mortem human brain: effects of post mortem interval, subject age, and Alzheimer's disease. *Neuroscience* **69**, 125-138.

[9] Hyman BT, Van Hoesen GW, Damasio AR, Barnes CL (1984) Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. *Science* **225**, 1168-1170.

[10] Bertholf RL (1987) Aluminum and Alzheimer's disease: perspectives for a cytoskeletal mechanism. *Crit Rev Clin Lab Sci* **25**, 195-210.

[11] Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M (2005) Global prevalence of dementia: a Delphi consensus study. *Lancet* **366**, 2112-2117.

[12] LaFerla FM (2002) Calcium dyshomeostasis and intracellular signalling in Alzheimer's disease. *Nat Rev Neurosci* **3**, 862-872.

[13] Annaert W, Cupers P, Saftig P, De Strooper B (2000) Presenilin function in APP processing. *Ann N Y Acad Sci* **920**, 158-164.

[14] Drago D, Bolognin S, Zatta P (2008) Role of metal ions in the abeta oligomerization in Alzheimer's disease and in other neurological disorders. *Curr Alzheimer Res* **5**, 500-507.

[15] Miu AC, Benga O (2006) Aluminum and Alzheimer's disease: a new look. *J Alzheimers Dis* **10**, 179-201.

[16] Lukiw WJ, Bazan NG (2000) Neuroinflammatory signaling upregulation in Alzheimer's disease. *Neurochem Res* **25**, 1173-1184.

[17] Pratico D, Delanty N (2000) Oxidative injury in diseases of the central nervous system: focus on Alzheimer's disease. *Am J Med* **109**, 577-585.

[18] Walton JR (1996) Amyloid, aluminium and the aetiology of Alzheimer's disease. *Med J Aust* **164**, 382-383.

[19] Joshi JG, Dhar M, Clauberg M, Chauthaiwale V (1994) Iron and aluminum homeostasis in neural disorders. *Environ Health Perspect* **102**(Suppl 3), 207-213.

[20] Matsuyama SS, Jarvik LF (1989) Hypothesis: microtubules, a key to Alzheimer disease. *Proc Natl Acad Sci U S A* **86**, 8152-8156.

[21] Pratico D, Uryu K, Leight S, Trojanoswki JQ, Lee VM (2001) Increased lipid peroxidation precedes amyloid

plaque formation in an animal model of Alzheimer amyloidosis. *J Neurosci* **21**, 4183-4187.

[22] Buxbaum JD, Ruefli AA, Parker CA, Cypess AM, Greengard P (1994) Calcium regulates processing of the Alzheimer amyloid protein precursor in a protein kinase C-independent manner. *Proc Natl Acad Sci U S A* **91**, 4489-4493.

[23] Kurumatani T, Fastbom J, Bonkale WL, Bogdanovic N, Winblad B, Ohm TG, Cowburn RF (1998) Loss of inositol 1,4,5-trisphosphate receptor sites and decreased PKC levels correlate with staging of Alzheimer's disease neurofibrillary pathology. *Brain Res* **796**, 209-221.

[24] Thompson K, Menzies S, Muckenthaler M, Torti FM, Wood T, Torti SV, Hentze MW, Beard J, Connor J (2003) Mouse brains deficient in H-ferritin have normal iron concentration but a protein profile of iron deficiency and increased evidence of oxidative stress. *J Neurosci Res* **71**, 46-63.

[25] Connor JR, Menzies SL, St Martin SM, Mufson EJ (1992) A histochemical study of iron, transferrin, and ferritin in Alzheimer's diseased brains. *J Neurosci Res* **31**, 75-83.

[26] Kell DB (2009) Iron behaving badly: inappropriate iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases. *BMC Med Genomics* **2**, 2.

[27] Yokel RA (2006) Blood-brain barrier flux of aluminum, manganese, iron and other metals suspected to contribute to metal-induced neurodegeneration. *J Alzheimers Dis* **10**, 223-253.

[28] Lumbreras M, Baamonde C, Martinez-Cue C, Lubec G, Cairns N, Salles J, Dierssen M, Florez J (2006) Brain G protein-dependent signaling pathways in Down syndrome and Alzheimer's disease. *Amino Acids* **31**, 449-456.

[29] Pratico D, Trojanowski JQ (2000) Inflammatory hypotheses: novel mechanisms of Alzheimer's neurodegeneration and new therapeutic targets? *Neurobiol Aging* **21**, 441-445; discussion 451-443.

[30] Nee LE, Eldridge R, Sunderland T, Thomas CB, Katz D, Thompson KE, Weingartner H, Weiss H, Julian C, Cohen R (1987) Dementia of the Alzheimer type: clinical and family study of 22 twin pairs. *Neurology* **37**, 359-363.

[31] Gupta VB, Anitha S, Hegde ML, Zecca L, Garruto RM, Ravid R, Shankar SK, Stein R, Shanmugavelu P, Jagannatha Rao KS (2005) Aluminium in Alzheimer's disease: are we still at a crossroad? *Cell Mol Life Sci* **62**, 143-158.

[32] Exley C (2001) *Aluminium and Alzheimer's Disease: The Science that Describes the Link*, Elsevier Science, Amsterdam, p. 452.

[33] Moore PB, Day JP, Taylor GA, Ferrier IN, Fifield LK, Edwardson JA (2000) Absorption of aluminium-26 in Alzheimer's disease, measured using accelerator mass spectrometry. *Dement Geriatr Cogn Disord* **11**, 66-69.

[34] Savory J, Exley C, Forbes WF, Huang Y, Joshi JG, Kruck T, McLachlan DR, Wakayama I (1996) Can the controversy of the role of aluminum in Alzheimer's disease be resolved? What are the suggested approaches to this controversy and methodological issues to be considered? *J Toxicol Environ Health* **48**, 615-635.

[35] Forbes WF, Hill GB (1998) Is exposure to aluminum a risk factor for the development of Alzheimer disease? – Yes. *Arch Neurol* **55**, 740-741.

[36] Munoz DG (1998) Is exposure to aluminum a risk factor for the development of Alzheimer disease? – No. *Arch Neurol* **55**, 737-739.

[37] Exley C, Korchazhkina O, Job D, Strekopytov S, Polwart A, Crome P (2006) Non-invasive therapy to reduce the body burden of aluminium in Alzheimer's disease. *J Alzheimers Dis* **10**, 17-24; discussion 29-31.

[38] ATSDR (2008) Toxicological profile for aluminum. Agency for toxic substances and disease registry, Atlanta, GA, p. 357, http://www.atsdr.cdc.gov/toxprofiles/tp22.html, Last Updated August 7, Accessed on July 4 2010.

[39] Carson (2000) Aluminum Compounds. Review of Toxicological Literature, Abridged Final Report, Integrated Laboratory Systems, Research Triangle Park, NC, p. 84, http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumpdf/Aluminum.pdf, Accessed on July 2010.

[40] Priest ND (1993) Satellite symposium on Alzheimer's disease and dietary aluminium. *Proc Nutr Soc* **52**, 231-240.

[41] McDermott JR, Smith AI, Iqbal K, Wisniewski HM (1979) Brain aluminum in aging and Alzheimer disease. *Neurology* **29**, 809-814.

[42] Perl DP, Brody AR (1980) Alzheimer's disease: X-ray spectrometric evidence of aluminum accumulation in neurofibrillary tangle-bearing neurons. *Science* **208**, 297-299.

[43] Kowall NW, Pendlebury WW, Kessler JB, Perl DP, Beal MF (1989) Aluminum-induced neurofibrillary degeneration affects a subset of neurons in rabbit cerebral cortex, basal forebrain and upper brainstem. *Neuroscience* **29**, 329-337.

[44] Edwardson JA, Candy JM, Ince PG, McArthur FK, Morris CM, Oakley AE, Taylor GA, Bjertness E (1992) Aluminium accumulation, beta-amyloid deposition and neurofibrillary changes in the central nervous system. *Ciba Found Symp* **169**, 165-179; discussion 179-185.

[45] Harrington CR, Wischik CM, McArthur FK, Taylor GA, Edwardson JA, Candy JM (1994) Alzheimer's-disease-like changes in tau protein processing: association with aluminium accumulation in brains of renal dialysis patients. *Lancet* **343**, 993-997.

[46] Perl DP, Moalem S (2006) Aluminum and Alzheimer's disease, a personal perspective after 25 years. *J Alzheimers Dis* **9**, 291-300.

[47] Walton JR (2006) Aluminum in hippocampal neurons from humans with Alzheimer's disease. *Neurotoxicology* **27**, 385-394.

[48] Walton JR (2009) Functional impairment in aged rats chronically exposed to human range dietary aluminum equivalents. *Neurotoxicology* **30**, 182-193.

[49] McLachlan DRC, Krishnan SS, Dalton AJ (1973) Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. *Science* **180**, 511-513.

[50] Matyja E (2000) Aluminum enhances glutamate-mediated neurotoxicity in organotypic cultures of rat hippocampus. *Folia Neuropathol* **38**, 47-53.

[51] Andrasi E, Pali N, Molnar Z, Kosel S (2005) Brain aluminum, magnesium and phosphorus contents of control and Alzheimer-diseased patients. *J Alzheimers Dis* **7**, 273-284.

[52] Uemura E (1984) Intranuclear aluminum accumulation in chronic animals with experimental neurofibrillary changes. *Exp Neurol* **85**, 10-18.

[53] Chafi AH, Hauw JJ, Rancurel G, Berry JP, Galle C (1991) Absence of aluminium in Alzheimer's disease brain tissue: electron microprobe and ion microprobe studies. *Neurosci Lett* **123**, 61-64.

[54] Landsberg JP, McDonald B, Watt F (1992) Absence of aluminium in neuritic plaque cores in Alzheimer's disease. *Nature* **360**, 65-68.

[55] Priest ND, Talbot RJ, Newton D, Day JP, King SJ, Fifield LK (1998) Uptake by man of aluminium in a public water supply. *Hum Exp Toxicol* **17**, 296-301.

[56] Gupta DM (2003) Renal osteodystrophy and aluminium bone disease in patients with chronic renal failure. *JK Practitioner* **10**, 107-111.
[57] Wills MR, Savory J (1985) Water content of aluminum, dialysis dementia, and osteomalacia. *Environ Health Perspect* **63**, 141-147.
[58] Shore D, Wyatt RJ (1983) Aluminum and Alzheimer's disease. *J Nerv Ment Dis* **171**, 553-558.
[59] McLachlan DRC, Quittkat S, Krishnan SS, Dalton AJ, De Boni U (1980) Intranuclear aluminum content in Alzheimer's disease, dialysis encephalopathy, and experimental aluminum encephalopathy. *Acta Neuropathol* **50**, 19-24.
[60] McLachlan DRC, Dalton AJ, Kruck TP, Bell MY, Smith WL, Kalow W, Andrews DF (1991) Intramuscular desferrioxamine in patients with Alzheimer's disease. *Lancet* **337**, 1304-1308.
[61] Walton JR (2007) A longitudinal study of rats chronically exposed to aluminum at human dietary levels. *Neurosci Lett* **412**, 29-33.
[62] Klaasen CD (1996) Heavy metals and heavy metal antagonists. In *Goodman & Gilson's The Pharmacological Basis of Therapeutics*, Hardman JG, Limbird LE, eds, McGraw-Hill, New York, pp. 1649-1672.
[63] Yokel RA, Allen DD, Meyer JJ (1994) Studies of aluminum neurobehavioral toxicity in the intact mammal. *Cell Mol Neurobiol* **14**, 791-808.
[64] Lai JC, Lim L, Davison AN (1982) Effects of Cd^{2+}, Mn^{2+}, and Al^{3+} on rat brain synaptosomal uptake of noradrenaline and serotonin. *J Inorg Biochem* **17**, 215-225.
[65] Lukiw WJ, Kruck TP, McLachlan DR (1987) Alterations in human linker histone-DNA binding in the presence of aluminum salts in vitro and in Alzheimer's disease. *Neurotoxicology* **8**, 291-301.
[66] Landsberg J, McDonald B, Grime G, Watt F (1993) Microanalysis of senile plaques using nuclear microscopy. *J Geriatr Psychiatry Neurol* **6**, 97-104.
[67] Walton J, Tuniz C, Fink D, Jacobsen G, Wilcox D (1995) Uptake of trace amounts of aluminum into the brain from drinking water. *Neurotoxicology* **16**, 187-190.
[68] Yokel RA (2002) Brain uptake, retention, and efflux of aluminum and manganese. *Environ Health Perspect* **110** (Suppl. 5), 699-704.
[69] King SJ, Oldham C, Popplewell JF, Carling RS, Day JP, Fifield LK, Cresswell RG, Liu K, di Tada ML (1997) Determination of aluminium-26 in biological materials by accelerator mass spectrometry. *Analyst* **122**, 1049-1055.
[70] Walton JR, Wang MX (2009) APP expression, distribution and accumulation are altered by aluminum in a rodent model for Alzheimer's disease. *J Inorg Biochem* **103**, 1548-1554.
[71] WHO (1998) Aluminium in Drinking-water. Background document for development of WHO Guidelines for drinking-water quality. In *Guidelines for Drinking-Water Quality*, 2nd ed., Addendum to Vol. 2. Health Health Criteria and Other Supporting Information, Geneva, p. 14, http://www.who.int/water_sanitation_health/dwq/chemicals/en/aluminium.pdf, Accessed on July 4 2010.
[72] Barabasz W, Albińska D, Jaśkowska M, Lipiec J (2002) Ecotoxicology of Aluminium. *Pol J Env Stud* **11**, 199-203.
[73] Miller RG, Kopfler FC, Kelty KC, Stober JA, Ulmer NS (1984) The occurrence of aluminum in drinking water. *J Am Water Works Assoc* **76**, 84-91.
[74] Plunkert PA (1998) Aluminum. Annual average primary aluminum price. *USMB*, 1-4, http://minerals.usgs.gov/minerals/pubs/commodity/aluminum/050798.pdf
[75] Zhang P, McCormick M, Hughes J (1994) Behaviour of aluminium during water treatment. In *Research report No. 85, Melbourne: Urban Water Research Association of Australia,* Melbourne, p. 135.
[76] Shovlin MG, Yoo RS, Crapper-McLachlan DR, Cummings E, Donohue JM, Hallman WK, Khachaturian Z, OrmeZavaleta J, Teefy S (1993) Aluminium in drinking water and Alzheimer's disease; a resource guide. In A*WWA Research Foundation and the American Water Works Association*, Denver, CO, pp. 7-8.
[77] Strunecka A, Strunecky O, Patocka J (2002) Fluoride plus aluminum: useful tools in laboratory investigations, but messengers of false information. *Physiol Res* **51**, 557-564.
[78] Strunecka A, Patocka J, Blaylock RL, Chinoy NJ (2007) Fluoride interactions: from molecules to diseases. *Curr Signal Transduct Ther* **2**, 190-213.
[79] Strunecka A, Patocka J (2002) *Aluminofluoride complexes: A Useful Tool in Laboratory Investigations, but a Hidden Danger for Living Organisms? ACS Symposium Series*, 822, American Chemical Society, pp. 271-282.
[80] Chen Y, Penington NJ (2000) Competition between internal AlF4-Stimulation of dorsal raphe neuron G-proteins coupled to calcium current inhibition. *J Neurophysiology* **83**, 1273-1282.
[81] Bigay J, Deterre P, Pfister C, Chabre M (1987) Fluoride complexes of aluminium or beryllium act on G-proteins as reversibly bound analogues of the gamma phosphate of GTP. *EMBO J* **6**, 2907-2913.
[82] Varner JA, Jensen KF, Horvath W, Isaacson RL (1998) Chronic administration of aluminum-fluoride or sodium-fluoride to rats in drinking water: alterations in neuronal and cerebrovascular integrity. *Brain Res* **784**, 284-298.
[83] Varner JA, Horvath WJ, Huie CW, Naslund HR, Isaacson RL (1994) Chronic aluminum fluoride administration. I. Behavioral observations. *Behav Neural Biol* **61**, 233-241.
[84] Ziegelbecker F (1998) Fluoridation in Europe. *Fluoride* **31**, 171-174.
[85] Alzheimer A (1907) Ueber einen eigenartige Erkrankung der Hirnrinde. *Zentralblatt fur Nervenheilkunde und Psychiatrie* **30**, 177-179.
[86] James GWB (1926) The treatment of senile insanity. *Lancet* **2**, 820-821.
[87] Shaw CA, Petrik MS (2009) Aluminum hydroxide injections lead to motor deficits and motor neuron degeneration. *J Inorg Biochem* **103**, 1555-1562.
[88] Yokel RA, Hicks CL, Florence RL (2008) Aluminum bioavailability from basic sodium aluminum phosphate, an approved food additive emulsifying agent, incorporated in cheese. *Food Chem Toxicol* **46**, 2261-2266.
[89] Saiyed SM, Yokel RA (2005) Aluminium content of some foods and food products in the USA, with aluminium food additives. *Food Addit Contam* **22**, 234-244.
[90] Lopez FE, Cabrera C, Lorenzo ML, Lopez MC (2002) Aluminum levels in convenience and fast foods: in vitro study of the absorbable fraction. *Sci Total Environ* **300**, 69-79.
[91] Rogers MA, Simon DG (1999) A preliminary study of dietary aluminium intake and risk of Alzheimer's disease. *Age Ageing* **28**, 205-209.
[92] Exley C (1998) Does antiperspirant use increase the risk of aluminium-related disease, including Alzheimer's disease? *Mol Med Today* **4**, 107-109.
[93] Greger JL, Sutherland JE (1997) Aluminum exposure and metabolism. *Crit Rev Clin Lab Sci* **34**, 439-474.
[94] Pennington JA, Schoen SA (1995) Estimates of dietary exposure to aluminium. *Food Addit Contam* **12**, 119-128.

[95] Dabeka RW, McKenzie AD (1990) Aluminium levels in Canadian infant formulate and estimation of aluminium intakes from formulae by infants 0–3 months old. *Food Addit Contam* **7**, 275-282.
[96] Gitelman HJ (1989) *Aluminum and Health: a Critical Review*, Dekker, New York.
[97] Pennington JA (1988) Aluminium content of foods and diets. *Food Addit Contam* **5**, 161-232.
[98] Gies WJ (1911) Some objections to the use of alum baking-powder. *JAMA* **57**, 816-821.
[99] Flaten TP (1990) Geographical associations between aluminum in drinking water and death rates with dementia (including Alzheimer's disease), Parkinson's disease and amyotrophic lateral sclerosis in Norway. *Environ Geochem Health* **12**, 152-167.
[100] McLachlan DRC, Bergeron C, Smith JE, Boomer D, Rifat SL (1996) Risk for neuropathologically confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential histories. *Neurology* **46**, 401-405.
[101] Rondeau V, Commenges D, Jacqmin-Gadda H, Dartigues JF (2000) Relation between aluminum concentrations in drinking water and Alzheimer's disease: an 8-year follow-up study. *Am J Epidemiol* **152**, 59-66.
[102] Rondeau V, Jacqmin-Gadda H, Commenges D, Helmer C, Dartigues JF (2009) Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. *Am J Epidemiol* **169**, 489-496.
[103] Martyn CN, Barker DJ, Osmond C, Harris EC, Edwardson JA, Lacey RF (1989) Geographical relation between Alzheimer's disease and aluminum in drinking water. *Lancet* **1**, 59-62.
[104] Jacqmin-Gadda H, Commenges D, Letenneur L, Dartigues JF (1996) Silica and aluminum in drinking water and cognitive impairment in the elderly. *Epidemiology* **7**, 281-285.
[105] 500Neri LC, Hewitt D (1991) Aluminium, Alzheimer's disease, and drinking water. *Lancet* **338**, 390.
[106] Gillette-Guyonnet S, Andrieu S, Nourhashemi F, de La Gueronniere V, Grandjean H, Vellas B (2005) Cognitive impairment and composition of drinking water in women: findings of the EPIDOS Study. *Am J Clin Nutr* **81**, 897-902.
[107] Campbell A, Becaria A, Lahiri DK, Sharman K, Bondy SC (2004) Chronic exposure to aluminum in drinking water increases inflammatory parameters selectively in the brain. *J Neurosci Res* **75**, 565-572.
[108] Flaten TP (2001) Aluminium as a risk factor in Alzheimer's disease, with emphasis on drinking water. *Brain Res Bull* **55**, 187-196.
[109] Greger JL (1993) Aluminum metabolism. *Annu Rev Nutr* **13**, 43-63.
[110] FAO/WHO (2006) Summary and conclusions of the sixty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), Sixty-seventh meeting in Rome, 20–29 June 2006, p. 11, http://www.who.int/ipcs/food/jecfa/jecfa67_call%20final.pdf, Issued July 7 2006, Accessed on July 2010.
[111] Zheng W (2001) Neurotoxicology of the brain barrier system: new implications. *J Toxicol Clin Toxicol* **39**, 711-719.
[112] Poole RL, Hintz SR, Mackenzie NI, Kerner JA Jr (2008) Aluminum exposure from pediatric parenteral nutrition: meeting the new FDA regulation. *J Parenter Enteral Nutr* **32**, 242-246.
[113] Newschaffer CJ, Croen LA, Daniels J, Giarelli E, Grether JK, Levy SE, Mandell DS, Miller LA, Pinto-Martin J, Reaven J, Reynolds AM, Rice CE, Schendel D, Windham GC (2007) The epidemiology of autism spectrum disorders. *Annu Rev Public Health* **28**, 235-258.
[114] Kogan MD, Blumberg SJ, Schieve LA, Boyle CA, Perrin JM, Ghandour RM, Singh GK, Strickland BB, Trevathan E, van Dyck PC (2009) Prevalence of parent-reported diagnosis of autism spectrum disorder among children in the US, 2007. *Pediatrics* **124**, 1395-1403.
[115] Baron-Cohen S, Scott FJ, Allison C, Williams J, Bolton P, Matthews FE, Brayne C (2009) Prevalence of autism-spectrum conditions: UK school-based population study. *Br J Psychiatry* **194**, 500-509.
[116] Offit PA, Jew RK (2003) Addressing parents' concerns: do vaccines contain harmful preservatives, adjuvants, additives, or residuals? *Pediatrics* **112**, 1394-1397.
[117] Flarend RE, Hem SL, White JL, Elmore D, Suckow MA, Rudy AC, Dandashli EA (1997) *In vivo* absorption of aluminium-containing vaccine adjuvants using 26Al. *Vaccine* **15**, 1314-1318.
[118] Yokel RA, McNamara PJ (2001) Aluminium toxicokinetics: an updated minireview. *Pharmacol Toxicol* **88**, 159-167.
[119] GlaxoSmithKline (2009) Boostrix product monograph, Combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine for booster vaccination, Date of Approval: October 21, 2009, http://www.gsk.ca/english/docs-pdf/Boostrix_PM_20091021_EN.pdf, Accessed on August 4 2010.
[120] Makidon PE, Bielinska AU, Nigavekar SS, Janczak KW, Knowlton J, Scott AJ, Mank N, Cao Z, Rathinavelu S, Beer MR, Wilkinson JE, Blanco LP, Landers JJ, Baker JR Jr (2008) Pre-clinical evaluation of a novel nanoemulsion-based hepatitis B mucosal vaccine. *PLoS One* **3**, e2954.
[121] Exley C (2009) Aluminium and medicine. In *Molecular and Supramolecular Bioinorganic Chemistry: Applications in Medical Sciences,* Merce ALR, Felcman J, Recio MAL, eds, Nova Biomedical Books, New York, pp. 45-68.
[122] Blaylock RL (2004) Excitotoxicity: a possible central mechanism in fluoride neurotoxicity. *Fluoride* **37**, 264-277.
[123] Gherardi RK (2003) Lessons from macrophagic myofasciitis: towards definition of a vaccine adjuvant-related syndrome. *Rev Neurol (Paris)* **159**, 162-164.
[124] Gherardi RK, Coquet M, Cherin P, Belec L, Moretto P, Dreyfus PA, Pellissier JF, Chariot P, Authier FJ (2001) Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle. *Brain* **124**, 1821-1831.
[125] Authier FJ, Cherin P, Creange A, Bonnotte B, Ferrer X, Abdelmoumni A, Ranoux D, Pelletier J, Figarella-Branger D, Granel B, Maisonobe T, Coquet M, Degos JD, Gherardi RK (2001) Central nervous system disease in patients with macrophagic myofasciitis. *Brain* **124**, 974-983.
[126] Exley C, Swarbrick L, Gherardi RK, Authier FJ (2009) A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome. *Med Hypotheses* **72**, 135-139.
[127] Israeli E, Agmon-Levin N, Blank M, Shoenfeld Y (2009) Adjuvants and autoimmunity. *Lupus* **18**, 1217-1225.
[128] Shoenfeld Y, Agmon-Levin N (2010) 'ASIA' – Autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun*, [Epub ahead of print] doi:10.1016/j.jaut.2010.07.003.
[129] Petrik MS, Wong MC, Tabata RC, Garry RF, Shaw CA (2007) Aluminum adjuvant linked to Gulf War illness induces motor neuron death in mice. *Neuromolecular Med* **9**, 83-100.

[130] Pennington JA, Jones JW (1989) Dietary intake of aluminum In A*luminum and health: a critical review,* Gitelman HJ, ed., Dekker, New York, pp. 67-101.
[131] Xiong JS, Branigan D, Li M (2009) Deciphering the MSG controversy. *Int J Clinical Exp Med* **2**, 329-336.
[132] Gonzalez-Burgos I, Velazquez-Zamora DA, Beas-Zarate C (2009) Damage and plasticity in adult rat hippocampal trisynaptic circuit neurons after neonatal exposure to glutamate excitotoxicity. *Int J Dev Neurosci* **27**, 741-745.
[133] Deloncle R, Fauconneau B, Piriou A, Huguet F, Guillard O (2002) Aluminum L-glutamate complex in rat brain cortex: *in vivo* prevention of aluminum deposit by magnesium D-aspartate. *Brain Res* **946**, 247-252.
[134] Deloncle R, Guillard O, Huguet F, Clanet F (1995) Modification of the blood-brain barrier through chronic intoxication by aluminum glutamate. Possible role in the etiology of Alzheimer's disease. *Biol Trace Elem Res* **47**, 227-233.
[135] Nayak P, Chatterjee AK (2003) Dietary protein restriction causes modification in aluminum-induced alteration in glutamate and GABA system of rat brain. *BMC Neurosci* **4**, 4.
[136] Cunat L, Lanhers MC, Joyeux M, Burnel D (2000) Bioavailability and intestinal absorption of aluminum in rats: effects of aluminum compounds and some dietary constituents. *Biol Trace Elem Res* **76**, 31-55.
[137] Mundy WR, Freudenrich TM, Kodavanti PR (1997) Aluminum potentiates glutamate-induced calcium accumulation and iron-induced oxygen free radical formation in primary neuronal cultures. *Mol Chem Neuropathol* **32**, 41-57.
[138] Sorenson JR, Campbell IR, Tepper LB, Lingg RD (1974) Aluminum in the environment and human health. *Environ Health Perspect* **8**, 3-95.
[139] Exley C (2004) Aluminum in antiperspirants: more than just skin deep. *Am J Med* **117**, 969-970.
[140] Guillard O, Fauconneau B, Olichon D, Dedieu G, Deloncle R (2004) Hyperaluminemia in a woman using an aluminum-containing antiperspirant for 4 years. *Am J Med* **117**, 956-959.
[141] Graves AB, White E, Koepsell TD, Reifler BV, van Belle G, Larson EB (1990) The association between aluminum-containing products and Alzheimer's disease. *J Clin Epidemiol* **43**, 35-44.
[142] FDA DHHS (2003) Skin Protectant Drug Products for Over-the-Counter Human Use, Final Monograph. *Fed Regist* **68**, 34273-34290.
[143] Alzheimer Society of Canada, Alzheimer's Disease, Causes of Alzheimer's Disease, http://www.alzheimer.ca/english/disease/causes-alumi.htm, Last updated March 2009, Accessed on August 4, 2010.
[144] Polizzi S, Pira E, Ferrara M, Bugiani M, Papaleo A, Albera R, Palmi S (2002) Neurotoxic effects of aluminium among foundry workers and Alzheimer's disease. *Neurotoxicology* **23**, 761-774.
[145] Sinczuk-Walczak H, Szymczak M, Razniewska G, Matczak W, Szymczak W (2003) Effects of occupational exposure to aluminum on nervous system: clinical and electroencephalographic findings. *Int J Occup Med Environ Health* **16**, 301-310.
[146] Joshi JG (1991) Neurochemical hypothesis: participation by aluminum in producing critical mass of colocalized errors in brain leads to neurological disease. *Comp Biochem Physiol C* **100**, 103-105.
[147] Shafer TJ, Mundy WR (1995) Effects of aluminum on neuronal signal transduction: mechanisms underlying disruption of phosphoinositide hydrolysis. *Gen Pharmacol* **26**, 889-895.
[148] Mundy WR, Kodavanti PR, Dulchinos VF, Tilson HA (1994) Aluminum alters calcium transport in plasma membrane and endoplasmic reticulum from rat brain. *J Biochem Toxicol* **9**, 17-23.
[149] Macdonald TL, Humphreys WG, Martin RB (1987) Promotion of tubulin assembly by aluminum ion in vitro. *Science* **236**, 183-186.
[150] McLachlan DRC, Farnell BJ (1986) Cellular mechanisms of aluminium toxicity. *Ann Ist Super Sanita* **22**, 697-702.
[151] Siegel N, Haug A (1983) Aluminum interaction with calmodulin. Evidence for altered structure and function from optical and enzymatic studies. *Biochim Biophys Acta* **744**, 36-45.
[152] Roskams AJ, Connor JR (1990) Aluminum access to the brain: a role for transferrin and its receptor. *Proc Natl Acad Sci U S A* **87**, 9024-9027.
[153] Silva VS, Duarte AI, Rego AC, Oliveira CR, Goncalves PP (2005) Effect of chronic exposure to aluminium on isoform expression and activity of rat (Na^+/K^+)ATPase. *Toxicol Sci* **88**, 485-494.
[154] Exley C, Price NC, Birchall JD (1994) Aluminum inhibition of hexokinase activity *in vitro*: a study in biological availability. *J Inorg Biochem* **54**, 297-304.
[155] Lukiw WJ (2001) Aluminum and gene transcription in the mammalian central nervous system-implications for Alzheimer's Disease. In A*luminium and Alzheimer's Disease: The science that describes the link,* Exley C, ed., Elsevier Science, Amsterdam, pp. 147-169.
[156] McLachlan DRC, Dam TV, Farnell BJ, Lewis PN (1983) Aluminum inhibition of ADP-ribosylation *in vivo* and *in vitro*. *Neurobehav Toxicol Teratol* **5**, 645-647.
[157] Lukiw WJ, LeBlanc HJ, Carver LA, McLachlan DR, Bazan NG (1998) Run-on gene transcription in human neocortical nuclei. Inhibition by nanomolar aluminum and implications for neurodegenerative disease. *J Mol Neurosci* **11**, 67-78.
[158] Cherroret G, Desor D, Hutin MF, Burnel D, Capolaghi B, Lehr PR (1996) Effects of aluminum chloride on normal and uremic adult male rats. Tissue distribution, brain choline acetyltransferase activity, and some biological variables. *Biol Trace Elem Res* **54**, 43-53.
[159] King RG (1984) Do raised brain aluminium levels in Alzheimer's dementia contribute to cholinergic neuronal deficits? *Med Hypotheses* **14**, 301-306.
[160] King RG, Sharp JA, Boura AL (1983) Aluminium, choline transportation and Alzheimer's disease. *Med J Aust* **2**, 606-607.
[161] Huber CT, Frieden E (1970) The inhibition of ferroxidase by trivalent and other metal ions. *J Biol Chem* **245**, 3979-3984.
[162] Abdel-Ghany M, el-Sebae AK, Shalloway D (1993) Aluminum-induced nonenzymatic phospho-incorporation into human tau and other proteins. *J Biol Chem* **268**, 11976-11981.
[163] Banks WA, Kastin AJ (1989) Aluminum-induced neurotoxicity: alterations in membrane function at the blood-brain barrier. *Neurosci Biobehav Rev* **13**, 47-53.
[164] Nehru B, Anand P (2005) Oxidative damage following chronic aluminium exposure in adult and pup rat brains. *J Trace Elem Med Biol* **19**, 203-208.
[165] Jing Y, Wang Z, Song Y (2004) Quantitative study of aluminum-induced changes in synaptic ultrastructure in rats. *Synapse* **52**, 292-298.

[166] Bondy SC, Ali SF, Guo-Ross S (1998) Aluminum but not iron treatment induces pro-oxidant events in the rat brain. *Mol Chem Neuropathol* **34**, 219-232.
[167] Jope RS, Johnson GV (1992) Neurotoxic effects of dietary aluminium. *Ciba Found Symp* **169**, 254-262; discussion 262-257.
[168] Johnson GV, Watson AL Jr, Lartius R, Uemura E, Jope RS (1992) Dietary aluminum selectively decreases MAP-2 in brains of developing and adult rats. *Neurotoxicology* **13**, 463-474.
[169] Bowdler NC, Beasley DS, Fritze EC, Goulette AM, Hatton JD, Hession J, Ostman DL, Rugg DJ, Schmittdiel CJ (1979) Behavioral effects of aluminum ingestion on animal and human subjects. *Pharmacol Biochem Behav* **10**, 505-512.
[170] Thorne BM, Donohoe T, Lin KN, Lyon S, Medeiros DM, Weaver ML (1986) Aluminum ingestion and behavior in the Long-Evans rat. *Physiol Behav* **36**, 63-67.
[171] Pivnick EK, Kerr NC, Kaufman RA, Jones DP, Chesney RW (1995) Rickets secondary to phosphate depletion. A sequela of antacid use in infancy. *Clin Pediatr (Phila)* **34**, 73-78.
[172] Fewtrell MS, Bishop NJ, Edmonds CJ, Isaacs EB, Lucas A (2009) Aluminum exposure from parenteral nutrition in preterm infants: bone health at 15-year follow-up. *Pediatrics* **124**, 1372-1379.
[173] Candy JM, Oakley AE, Mountfort SA, Taylor GA, Morris CM, Bishop HE, Edwardson JA (1992) The imaging and quantification of aluminium in the human brain using dynamic secondary ion mass spectrometry (SIMS). *Biol Cell* **74**, 109-118.
[174] Lukiw WJ, Krishnan B, Wong L, Kruck TP, Bergeron C, Crapper McLachlan DR (1992) Nuclear compartmentalization of aluminum in Alzheimer's disease (AD). *Neurobiol Aging* **13**, 115-121.
[175] Yokel RA, Allen DD, Ackley DC (1999) The distribution of aluminum into and out of the brain. *J Inorg Biochem* **76**, 127-132.
[176] Exley C, Burgess E, Day JP, Jeffery EH, Melethil S, Yokel RA (1996) Aluminum toxicokinetics. *J Toxicol Environ Health* **48**, 569-584.
[177] French P, Gardner MJ, Gunn M (1989) Dietary aluminium and Alzheimer's disease. *Food Chem Toxicol* **27**, 495-496.
[178] Wenk GL, Stemmer KL (1981) The influence of ingested aluminum upon norepinephrine and dopamine levels in the rat brain. *Neurotoxicology* **2**, 347-353.
[179] Abreo K (2001) Aluminum-induced bone disease: implications for Alzheimer's disease. In A*luminium and Alzheimer's Disease: The science that describes the link,* Exley C, ed., Elsevier Science, Amsterdam, pp. 37-59.
[180] D'Haese PC, Couttenye MM, De Broe ME (1996) Diagnosis and treatment of aluminium bone disease. *Nephrol Dial Transplant* **11**(Suppl 3), 74-79.
[181] Ebersole PS, Hess PA, Luggen AS (2004) Age-related changes: renal changes. In *Toward Healthy Aging: Human Needs and Nursing Response,* Ledbetter MS, Gower LK, eds, Mosby Inc. St Louis, MO, p. 89.
[182] Lukiw WJ, Kruck TP, McLachlan DR (1989) Linker histone-DNA complexes: enhanced stability in the presence of aluminum lactate and implications for Alzheimer's disease. *FEBS Lett* **253**, 59-62.
[183] McLachlan DRC, Lukiw WJ, Mizzen CA, Kruck TP (1989) Chromatin structure in Alzheimer's disease: effect on 5′ leader sequence for NF-L gene and role of aluminum. *Prog Clin Biol Res* **317**, 1061-1075.
[184] McLachlan DRC, Lukiw WJ, Kruck TP (1989) New evidence for an active role of aluminum in Alzheimer's disease. *Can J Neurol Sci* **16**, 490-497.
[185] McLachlan DRC, Lukiw WJ, Kruck TPA (1990) Aluminum, altered transcription, and the pathogenesis of Alzheimer's disease. *Env Geochem Health* **12**, 103-114.
[186] Mann DM (1996) Pyramidal nerve cell loss in Alzheimer's disease. *Neurodegeneration* **5**, 423-427.
[187] Heckers S, Geula C, Mesulam MM (1992) Acetylcholinesterase-rich pyramidal neurons in Alzheimer's disease. *Neurobiol Aging* **13**, 455-460.
[188] Salimi I, Friel KM, Martin JH (2008) Pyramidal tract stimulation restores normal corticospinal tract connections and visuomotor skill after early postnatal motor cortex activity blockade. *J Neurosci* **28**, 7426-7434.
[189] Elston GN (2003) Cortex, cognition and the cell: new insights into the pyramidal neuron and prefrontal function. *Cereb Cortex* **13**, 1124-1138.
[190] Connor JR, Snyder BS, Arosio P, Loeffler DA, LeWitt P (1995) A quantitative analysis of isoferritins in select regions of aged, parkinsonian, and Alzheimer's diseased brains. *J Neurochem* **65**, 717-724.
[191] Favarato M, Mizzen CA, McLachlan DR (1992) Resolution of serum aluminum-binding proteins by size-exclusion chromatography: identification of a new carrier of aluminum in human serum. *J Chromatogr* **576**, 271-285.
[192] Day JP, Barker J, Evans LJA, Perks J, Seabright PJ, Ackrill P, Lilley JS, Drumm PV, Newton GWA (1991) Aluminium absorption studied by 26Al tracer. *Lancet* **337**, 1345.
[193] Favarato M, Mizzen C, Kruck TPA (1990) Chromatographic resolution of aluminum binding components in human serum. *Neurobiol Aging* **11**, 315.
[194] Beardmore J, Exley C (2009) Towards a model of non-equilibrium binding of metal ions in biological systems. *J Inorg Biochem* **103**, 205-209.
[195] Moos T, Morgan EH (2000) Transferrin and transferrin receptor function in brain barrier systems. *Cell Mol Neurobiol* **20**, 77-95.
[196] Morris CM, Candy JM, Kerwin JM, Edwardson JA (1994) Transferrin receptors in the normal human hippocampus and in Alzheimer's disease. *Neuropathol Appl Neurobiol* **20**, 473-477.
[197] Pardridge WM, Eisenberg J, Yang J (1987) Human blood-brain barrier transferrin receptor. *Metabolism* **36**, 892-895.
[198] Sakajiri T, Yamamura T, Kikuchi T, Ichimura K, Sawada T, Yajima H (2009) Absence of binding between the human transferrin receptor and the transferrin complex of biological toxic trace element, aluminum, because of an incomplete open/closed form of the complex. *Biol Trace Elem Res* **136**, 279-286.
[199] Ha-Duong NT, Hemadi M, Chikh Z, Chahine JM (2008) Kinetics and thermodynamics of metal-loaded transferrins: transferrin receptor 1 interactions. *Biochem Soc Trans* **36**, 1422-1426.
[200] Hemadi M, Miquel G, Kahn PH, El Hage Chahine JM (2003) Aluminum exchange between citrate and human serum transferrin and interaction with transferrin receptor 1. *Biochemistry* **42**, 3120-3130.
[201] Smans KA, D'Haese PC, Van Landeghem GF, Andries LJ, Lamberts LV, Hendy GN, De Broe ME (2000) Transferrin-mediated uptake of aluminium by human parathyroid cells results in reduced parathyroid hormone secretion. *Nephrol Dial Transplant* **15**, 1328-1336.

[202] McGregor SJ, Brock JH, Halls D (1991) The role of transferrin and citrate in cellular uptake of aluminium. *Biol Met* **4**, 173-175.
[203] McGregor SJ, Naves ML, Birly AK, Russell NH, Halls D, Junor BJ, Brock JH (1991) Interaction of aluminium and gallium with human lymphocytes: the role of transferrin. *Biochim Biophys Acta* **1095**, 196-200.
[204] Abreo K, Jangula J, Jain SK, Sella M, Glass J (1991) Aluminum uptake and toxicity in cultured mouse hepatocytes. *J Am Soc Nephrol* **1**, 1299-1304.
[205] Fleming J, Joshi JG (1987) Ferritin: isolation of aluminum-ferritin complex from brain. *Proc Natl Acad Sci U S A* **84**, 7866-7870.
[206] Dedman DJ, Treffry A, Candy JM, Taylor GA, Morris CM, Bloxham CA, Perry RH, Edwardson JA, Harrison PM (1992) Iron and aluminium in relation to brain ferritin in normal individuals and Alzheimer's-disease and chronic renal-dialysis patients. *Biochem J* **287**(Pt 2), 509-514.
[207] Spada PL, Rossi C, Alimonti A, Bocca B, Ricerca BM, Bocci MG, Carvelli M, Vulpio C, Luciani G, De Sole P (2009) Iron, zinc and aluminium ferritin content of hemodialysis hyperferritinemic patients: comparison with other hyperferritinemic clinical conditions and normoferritinemic blood donors. *Clin Biochem* **42**, 1654-1657.
[208] Brewer GJ (2007) Iron and copper toxicity in diseases of aging, particularly atherosclerosis and Alzheimer's disease. *Exp Biol Med (Maywood)* **232**, 323-335.
[209] Alexandrov PN, Zhao Y, Pogue AI, Tarr MA, Kruck TP, Percy ME, Cui JG, Lukiw WJ (2005) Synergistic effects of iron and aluminum on stress-related gene expression in primary human neural cells. *J Alzheimers Dis* **8**, 117-127; discussion 209-115.
[210] Smith MA, Harris PL, Sayre LM, Perry G (1997) Iron accumulation in Alzheimer disease is a source of redox-generated free radicals. *Proc Natl Acad Sci U S A* **94,** 9866-9868.
[211] Exley C (2004) The pro-oxidant activity of aluminum. *Free Radic Biol Med* **36**, 380-387.
[212] Verstraeten SV, Golub MS, Keen CL, Oteiza PI (1997) Myelin is a preferential target of aluminum-mediated oxidative damage. *Arch Biochem Biophys* **344**, 289-294.
[213] Khan A, Dobson JP, Exley C (2006) Redox cycling of iron by Abeta42. *Free Radic Biol Med* **40**, 557-569.
[214] Floyd RA (1999) Antioxidants, oxidative stress, and degenerative neurological disorders. *Proc Soc Exp Biol Med* **222**, 236-245.
[215] Olanow CW (1993) A radical hypothesis for neurodegeneration. *Trends Neurosci* **16**, 439-444.
[216] Pandya JD, Dave KR, Katyare SS (2004) Effect of long-term aluminum feeding on lipid/phospholipid profiles of rat brain myelin. *Lipids Health Dis* **3**, 13.
[217] Sokoloff L (1981) Relationships among local functional activity, energy metabolism, and blood flow in the central nervous system. *Fed Proc* **40,** 2311-2316.
[218] Maker HS, Clarke DD, Lajtha AL (1972) Intermediary metabolism of carbohydrates and amino acids. In *Basic Neurochemistry,* Siegal GL, Albers RW, Katzman R, Agranoff BW, eds, Little, Brown and Co., Boston, pp. 279-307.
[219] Johnson GV, Jope RS (1986) Aluminum impairs glucose utilization and cholinergic activity in rat brain *in vitro*. *Toxicology* **40**, 93-102.
[220] McLachlan DRC, Dalton AJ (1973) Alterations in short-term retention, conditioned avoidance response acquisition and motivation following aluminum induced neurofibrillary degeneration. *Physiol Behav* **10**, 925-933.
[221] Hellwig B (1993) How the myelin picture of the human cerebral cortex can be computed from cytoarchitectural data. A bridge between von Economo and Vogt. *J Hirnforsch* **34**, 387-402.
[222] Lintl P, Braak H (1983) Loss of intracortical myelinated fibers: a distinctive age-related alteration in the human striate area. *Acta Neuropathol* **61**, 178-182.
[223] Grant P, Pant HC (2000) Neurofilament protein synthesis and phosphorylation. *J Neurocytol* **29**, 843-872.
[224] Shea TB, Beermann ML (1994) Respective roles of neurofilaments, microtubules, MAP1B, and tau in neurite outgrowth and stabilization. *Mol Biol Cell* **5**, 863-875.
[225] Jicha GA, Weaver C, Lane E, Vianna C, Kress Y, Rockwood J, Davies P (1999) cAMP-dependent protein kinase phosphorylations on tau in Alzheimer's disease. *J Neurosci* **19**, 7486-7494.
[226] Blanchard BJ, devi Raghunandan R, Roder HM, Ingram VM (1994) Hyperphosphorylation of human TAU by brain kinase PK40erk beyond phosphorylation by cAMP-dependent PKA: relation to Alzheimer's disease. *Biochem Biophys Res Commun* **200**, 187-194.
[227] el-Sebae AH, Abdel-Ghany ME, Shalloway D, Abou Zeid MM, Blancato J, Saleh MA (1993) Aluminum interaction with human brain tau protein phosphorylation by various kinases. *J Environ Sci Health B* **28**, 763-777.
[228] Markesbery WR (1999) The role of oxidative stress in Alzheimer disease. *Arch Neurol* **56**, 1449-1452.
[229] Markesbery WR, Carney JM (1999) Oxidative alterations in Alzheimer's disease. *Brain Pathol* **9**, 133-146.
[230] Gomez M, Esparza JL, Nogues MR, Giralt M, Cabre M, Domingo JL (2005) Pro-oxidant activity of aluminum in the rat hippocampus: gene expression of antioxidant enzymes after melatonin administration. *Free Radic Biol Med* **38**, 104-111.
[231] Pratico D, Uryu K, Sung S, Tang S, Trojanowski JQ, Lee VM (2002) Aluminum modulates brain amyloidosis through oxidative stress in APP transgenic mice. *FASEB J* **16**, 1138-1140.
[232] Bondy SC, Liu D, Guo-Ross S (1998) Aluminum treatment induces nitric oxide synthase in the rat brain. *Neurochem Int* **33**, 51-54.
[233] Pratico D, Rokach J, Lawson J, Fitzgerald GA (2004) F2-isoprostanes as indices of lipid peroxidation in inflammatory diseases. *Chem Phys Lipids* **128**, 165-171.
[234] Pratico D, Clark CM, Lee VM, Trojanowski JQ, Rokach J, Fitzgerald GA (2000) Increased 8,12-*iso*-iPF2alpha-VI in Alzheimer's disease: correlation of a noninvasive index of lipid peroxidation with disease severity. *Ann Neurol* **48**, 809-812.
[235] Pratico D, V MYL, Trojanowski JQ, Rokach J, Fitzgerald GA (1998) Increased F2-isoprostanes in Alzheimer's disease: evidence for enhanced lipid peroxidation *in vivo*. *FASEB J* **12**, 1777-1783.
[236] Wu J, Du F, Zhang P, Khan IA, Chen J, Liang Y (2005) Thermodynamics of the interaction of aluminum ions with DNA: implications for the biological function of aluminum. *J Inorg Biochem* **99**, 1145-1154.
[237] Lukiw WJ, Percy ME, Kruck TP (2005) Nanomolar aluminum induces pro-inflammatory and pro-apoptotic gene expression in human brain cells in primary culture. *J Inorg Biochem* **99**, 1895-1898.
[238] Ripovi D, Platilova V, Strunecka A, Jirak R, Hoschl C (2000) Cytosolic calcium alterations in platelets of patients with early stages of Alzheimer's disease. *Neurobiol Aging* **21**, 729-734.

[239] Grammas P, Roher AE, Ball MJ (1994) Increased accumulation of cAMP in cerebral microvessels in Alzheimer's disease. *Neurobiol Aging* **15**, 113-116.

[240] Young-Pearse TL, Chen AC, Chang R, Marquez C, Selkoe DJ (2008) Secreted APP regulates the function of full-length APP in neurite outgrowth through interaction with integrin beta1. *Neural Dev* **3**, 15.

[241] De Strooper B, Annaert W (2000) Proteolytic processing and cell biological functions of the amyloid precursor protein. *J Cell Sci* **113** (Pt 11), 1857-1870.

[242] Bell KF, Zheng L, Fahrenholz F, Cuello AC (2008) ADAM-10 over-expression increases cortical synaptogenesis. *Neurobiol Aging* **29**, 554-565.

[243] Alzheimer's Association (alz.org), Alzheimer Myths, http://www.alz.org/alzheimers_disease_myths_about_alzheimers.asp, Last Updated January 4, 2010, Accessed on August 4, 2010.

[244] Alzheimer's Association (alz.org), Association responds to USA TODAY letter to the editor, http://www.alz.org/news_and_events_alzheimer_news_02-02-2005.asp, Last Updated December 22, 2006, Accessed on August 4, 2010.

[245] McLachlan DRC (1995) Aluminium and the risk for alzheimer's disease. *Environmetrics* **6**, 233-275.

[246] McLachlan DRC, Kruck TP, Lukiw WJ, Krishnan SS (1991) Would decreased aluminum ingestion reduce the incidence of Alzheimer's disease? *CMAJ* **145**, 793-804.

[247] Perl DP (2001) The association of aluminum and neurofibrillary degeneration in Alzheimer's Disease, a personal perspective. In A*luminium and Alzheimer's Disease: The science that describes the link,* Exley C, ed., Elsevier Science, Amsterdam, pp. 133-147.

[248] Altmann P (2001) Aluminium induced disease in subjects with and without renal failure-does it help us understand the role of aluminium in Alzheimer's Disease? In *Aluminium and Alzheimer's Disease: The Science that Describes the Link,* Exley C, ed., Elsevier Science, Amsterdam, pp. 1-37.

[249] Golub MS (2001) Behavioral studies in animals: past and potential contribution to the understanding of the relationship between aluminium and Alzheimer's Disease. In *Aluminium and Alzheimer's Disease: The Science that Describes the Link,* Exley C, ed., Elsevier Science, Amsterdam, pp. 169-189.

[250] Pendlebury WW, Beal MF, Kowall NW, Solomon PR (1988) Neuropathologic, neurochemical and immunocytochemical characteristics of aluminum-induced neurofilamentous degeneration. *Neurotoxicology* **9**, 503-510.

[251] Rozas VV, Port FK, Easterling RE (1978) An outbreak of dialysis dementia due to aluminum in the dialysate. *J Dial* **2**, 459-470.

[252] Flendrig JA, Kruis H, Das HA (1976) Aluminium intoxication: the cause of dialysis dementia? *Proc Eur Dial Transplant Assoc* **13**, 355-368.

[253] McLachlan DRC, Tomko GJ (1975) Neuronal correlates of an encephalopathy associated with aluminum neurofibrillary degeneration. *Brain Res* **97**, 253-264.

[254] Platt B, Carpenter DO, Busselberg D, Reymann KG, Riedel G (1995) Aluminum impairs hippocampal long-term potentiation in rats *in vitro* and *in vivo*. *Exp Neurol* **134**, 73-86.

[255] Beal MF, Mazurek MF, Ellison DW, Kowall NW, Solomon PR, Pendlebury WW (1989) Neurochemical characteristics of aluminum-induced neurofibrillary degeneration in rabbits. *Neuroscience* **29**, 339-346.

[256] Zatta P, Ibn-Lkhayat-Idrissi M, Zambenedetti P, Kilyen M, Kiss T (2002) *In vivo* and *in vitro* effects of aluminum on the activity of mouse brain acetylcholinesterase. *Brain Res Bull* **59**, 41-45.

[257] Moraes MS, Leite SR (1994) Inhibition of bovine brain acetylcholinesterase by aluminum. *Braz J Med Biol Res* **27**, 2635-2638.

[258] Patocka J, Bajgar J (1987) Aluminium activation and inhibition of human brain acetylcholinesterase *in vitro. Inorg Chim Acta* **135***,* 161-163.

[259] Lai JC, Guest JF, Leung TK, Lim L, Davison AN (1980) The effects of cadmium, manganese and aluminium on sodium-potassium-activated and magnesium-activated adenosine triphosphatase activity and choline uptake in rat brain synaptosomes. *Biochem Pharmacol* **29**, 141-146.

[260] Cucarella C, Montoliu C, Hermenegildo C, Saez R, Manzo L, Minana MD, Felipo V (1998) Chronic exposure to aluminum impairs neuronal glutamate-nitric oxide-cyclic GMP pathway. *J Neurochem* **70**, 1609-1614.

[261] Meiri H, Banin E, Roll M, Rousseau A (1993) Toxic effects of aluminium on nerve cells and synaptic transmission. *Prog Neurobiol* **40**, 89-121.

[262] Rao KS (1990) Effects of aluminium salts on synaptosomal enzymes – an *in vitro* kinetic study. *Biochem Int* **22**, 725-734.

[263] Wong PC, Lai JC, Lim L, Davison AN (1981) Selective inhibition of L-glutamate and gammaaminobutyrate transport in nerve ending particles by aluminium, manganese, and cadmium chloride. *J Inorg Biochem* **14**, 253-260.

[264] Altindag ZZ, Baydar T, Engin AB, Sahin G (2003) Effects of the metals on dihydropteridine reductase activity. *Toxicol In Vitro* **17**, 533-537.

[265] Shafer TJ, Nostrandt AC, Tilson HA, Mundy WR (1994) Mechanisms underlying AlCl3 inhibition of agonist-stimulated inositol phosphate accumulation. Role of calcium, G-proteins, phospholipase C and protein kinase C. *Biochem Pharmacol* **47**, 1417-1425.

[266] Shafer TJ, Mundy WR, Tilson HA (1993) Aluminum decreases muscarinic, adrenergic, and metabotropic receptor-stimulated phosphoinositide hydrolysis in hippocampal and cortical slices from rat brain. *Brain Res* **629**, 133-140.

[267] Cochran M, Elliott DC, Brennan P, Chawtur V (1990) Inhibition of protein kinase C activation by low concentrations of aluminium. *Clin Chim Acta* **194**, 167-172.

[268] Koenig ML, Jope RS (1987) Aluminum inhibits the fast phase of voltage-dependent calcium influxes into synaptosomes. *J Neurochem* **49**, 316-320.

[269] Siegel N, Suhayda C, Haug A (1982) Aluminum changes the conformation of calmodulin. *Physiol Chem Phys* **14**, 165-167.

[270] Beal MF, Hyman BT, Koroshetz W (1993) Do defects in mitochondrial energy metabolism underlie the pathology of neurodegenerative diseases? *Trends Neurosci* **16**, 125-131.

[271] Drago D, Cavaliere A, Mascetra N, Ciavardelli D, di Ilio C, Zatta P, Sensi SL (2008) Aluminum modulates effects of beta amyloid(1-42) on neuronal calcium homeostasis and mitochondria functioning and is altered in a triple transgenic mouse model of Alzheimer's disease. *Rejuvenation Res* **11**, 861-871.

[272] Lipman JJ, Colowick SP, Lawrence PL, Abumrad NN (1988) Aluminum induced encephalopathy in the rat. *Life Sci* **42**, 863-875.

[273] Li X, Zheng H, Zhang Z, Li M, Huang Z, Schluesener HJ, Li Y, Xu S (2009) Glia activation induced by peripheral administration of aluminum oxide nanoparticles in rat brains. *Nanomed Nanotech Biol Med* **5**, 473-479.

[274] Muma NA, Troncoso JC, Hoffman PN, Koo EH, Price DL (1988) Aluminum neurotoxicity: altered expression of cytoskeletal genes. *Brain Res* **427**, 115-121.
[275] McLachlan DRC, Krishnan SS, Quittkat S (1976) Aluminium, neurofibrillary degeneration and Alzheimer's disease. *Brain* **99**, 67-80.
[276] Humphreys WG, Macdonald TL (1988) The effects on tubulin polymerization and associated guanosine triphosphate hydrolysis of aluminum ion, fluoride and fluoroaluminate species. *Biochem Biophys Res Commun* **151**, 1025-1032.
[277] Shea TB, Beermann ML, Nixon RA (1995) Aluminum treatment of intact neuroblastoma cells alters neurofilament subunit phosphorylation, solubility, and proteolysis. *Mol Chem Neuropathol* **26**, 1-14.
[278] Shin RW, Kruck TP, Murayama H, Kitamoto T (2003) A novel trivalent cation chelator Feralex dissociates binding of aluminum and iron associated with hyperphosphorylated tau of Alzheimer's disease. *Brain Res* **961**, 139-146.
[279] Shin RW, Lee VM, Trojanowski JQ (1994) Aluminum modifies the properties of Alzheimer's disease PHF tau proteins *in vivo* and *in vitro*. *J Neurosci* **14**, 7221-7233.
[280] Yamamoto H, Saitoh Y, Yasugawa S, Miyamoto E (1990) Dephosphorylation of tau factor by protein phosphatase 2A in synaptosomal cytosol fractions, and inhibition by aluminum. *J Neurochem* **55**, 683-690.
[281] Exley C (2006) Aluminium and iron, but neither copper nor zinc, are key to the precipitation of beta-sheets of Abeta_{42} in senile plaque cores in Alzheimer's disease. *J Alzheimers Dis* **10**, 173-177.
[282] Exley C, Price NC, Kelly SM, Birchall JD (1993) An interaction of beta-amyloid with aluminium in vitro. *FEBS Lett* **324**, 293-295.
[283] Fasman GD, Perczel A, Moore CD (1995) Solubilization of beta-amyloid-(1-42)-peptide: reversing the beta-sheet conformation induced by aluminum with silicates. *Proc Natl Acad Sci U S A* **92**, 369-371.
[284] Exley C, Korchazhkina OV (2001) Promotion of formation of amyloid fibrils by aluminium adenosine triphosphate (AlATP). *J Inorg Biochem* **84**, 215-224.
[285] Kawahara M, Kato M, Kuroda Y (2001) Effects of aluminum on the neurotoxicity of primary cultured neurons and on the aggregation of beta-amyloid protein. *Brain Res Bull* **55**, 211-217.
[286] Drago D, Bettella M, Bolognin S, Cendron L, Scancar J, Milacic R, Ricchelli F, Casini A, Messori L, Tognon G, Zatta P (2008) Potential pathogenic role of beta-amyloid(1-42)-aluminum complex in Alzheimer's disease. *Int J Biochem Cell Biol* **40**, 731-746.
[287] Mills J, Laurent Charest D, Lam F, Beyreuther K, Ida N, Pelech SL, Reiner PB (1997) Regulation of amyloid precursor protein catabolism involves the mitogen-activated protein kinase signal transduction pathway. *J Neurosci* **17**, 9415-9422.
[288] Nitsch RM, Slack BE, Wurtman RJ, Growdon JH (1992) Release of Alzheimer amyloid precursor derivatives stimulated by activation of muscarinic acetylcholine receptors. *Science* **258**, 304-307.
[289] Xu H, Greengard P, Gandy S (1995) Regulated formation of Golgi secretory vesicles containing Alzheimer beta-amyloid precursor protein. *J Biol Chem* **270**, 23243-23245.
[290] Arribas J, Massague J (1995) Transforming growth factor-alpha and beta-amyloid precursor protein share a secretory mechanism. *J Cell Biol* **128**, 433-441.
[291] Sakamoto T, Saito H, Ishii K, Takahashi H, Tanabe S, Ogasawara Y (2006) Aluminum inhibits proteolytic degradation of amyloid beta peptide by cathepsin D: a potential link between aluminum accumulation and neuritic plaque deposition. *FEBS Lett* **580**, 6543-6549.
[292] Alfrey AC (1986) Dialysis encephalopathy. *Kidney Int Suppl* **18**, S53-S57.
[293] Alfrey AC (1978) Dialysis encephalopathy syndrome. *Annu Rev Med* **29**, 93-98.
[294] Alfrey AC, LeGendre GR, Kaehny WD (1976) The dialysis encephalopathy syndrome. Possible aluminum intoxication. *N Engl J Med* **294**, 184-188.
[295] Wisniewski HM, Sturman JA, Shek JW (1982) Chronic model of neurofibrillary changes induced in mature rabbits by metallic aluminum. *Neurobiol Aging* **3**, 11-22.
[296] Petit TL, Biederman GB, McMullen PA (1980) Neurofibrillary degeneration, dendritic dying back, and learning-memory deficits after aluminum administration: implications for brain aging. *Exp Neurol* **67**, 152-162.
[297] McLachlan DC (1973) Experimental neurofibrillary degeneration and altered electrical activity. *Electroencephalogr Clin Neurophysiol* **35**, 575-588.
[298] Klatzo I, Wisniewski H, Streicher E (1965) Experimental production of neurofibrillary degeneration. I. Light microscopic observations. *J Neuropathol Exp Neurol* **24**, 187-199.
[299] Shigematsu K, McGeer PL (1992) Accumulation of amyloid precursor protein in damaged neuronal processes and microglia following intracerebral administration of aluminum salts. *Brain Res* **593**, 117-123.
[300] Hewitt CD, Herman MM, Lopes MB, Savory J, Wills MR (1991) Aluminium maltol-induced neurocytoskeletal changes in fetal rabbit midbrain in matrix culture. *Neuropathol Appl Neurobiol* **17**, 47-60.
[301] Wisniewski H, Narkiewicz O, Wisniewska K (1967) Topography and dynamics of neurofibrillar degeneration in aluminum encephalopathy. *Acta Neuropathol* **9**, 127-133.
[302] Savory J, Huang Y, Wills MR, Herman MM (1998) Reversal by desferrioxamine of tau protein aggregates following two days of treatment in aluminum-induced neurofibrillary degeneration in rabbit: implications for clinical trials in Alzheimer's disease. *Neurotoxicology* **19**, 209-214.
[303] Selkoe DJ, Liem RK, Yen SH, Shelanski ML (1979) Biochemical and immunological characterization of neurofilaments in experimental neurofibrillary degeneration induced by aluminum. *Brain Res* **163**, 235-252.
[304] Gambetti P, Autilio-Gambetti L, Perry G, Shecket G, Crane RC (1983) Antibodies to neurofibrillary tangles of Alzheimer's disease raised from human and animal neurofilament fractions. *Lab Invest* **49**, 430-435.
[305] Walton JR (2007) An aluminum-based rat model for Alzheimer's disease exhibits oxidative damage, inhibition of PP2A activity, hyperphosphorylated tau, and granulovacuolar degeneration. *J Inorg Biochem* **101**, 1275-1284.
[306] Exley C, Esiri MM (2006) Severe cerebral congophilic angiopathy coincident with increased brain aluminium in a resident of Camelford, Cornwall, UK. *J Neurol Neurosurg Psychiatry* **77**, 877-879.
[307] Yumoto S, Kakimi S, Ohsaki A, Ishikawa A (2009) Demonstration of aluminum in amyloid fibers in the cores of senile plaques in the brains of patients with Alzheimer's disease. *J Inorg Biochem* **103**, 1579-1584.
[308] Walton JR, Diamond TH, Kumar S, Murrell GA (2007) A sensitive stain for aluminum in undecalcified cancellous bone. *J Inorg Biochem* **101**, 1285-1290.
[309] Kruck TP, Cui JG, Percy ME, Lukiw WJ (2004) Molecular shuttle chelation: the use of ascorbate, desferrioxamine

and Feralex-G in combination to remove nuclear bound aluminum. *Cell Mol Neurobiol* **24**, 443-459.

[310] Bertholf RL, Roman JM, Brown S, Savory J, Wills MR (1984) Aluminum hydroxide-induced osteomalacia, encephalopathy, and hyperaluminemia in CAPD. Treatment with desfenioxamine. *Perit Dial Int* **4**, 30-32.

[311] Williams P, Khanna R, Crapper McLachlan DR (1981) Enhancement of aluminum removal by desfemoxamine in a patient on continuous ambulatory peritoneal dialysis with dementia. *Perit Dial Int* **1**, 73.

[312] Flarend R (2001) Absorption of aluminum from antiperspirants and vaccine adjuvants. In *Aluminium and Alzheimer's Disease: The Science that Describes the Link,* Exley C, ed., Elsevier Science, Amsterdam, pp. 75-97.

[313] Flarend R, Bin T, Elmore D, Hem SL (2001) A preliminary study of the dermal absorption of aluminium from antiperspirants using aluminium-26. *Food Chem Toxicol* **39**, 163-168.

[314] Autret-Leca E, Bensouda-Grimaldi L, Jonville-Bera AP, Beau-Salinas F (2006) Pharmacovigilance of vaccines. *Arch Pediatrie* **13**, 175-180.

[315] Koo WW, Kaplan LA, Krug-Wispe SK (1988) Aluminum contamination of infant formulas. *J Parenter Enteral Nutr* **12**, 170-173.

[316] CDC, Recommended Immunization Schedule for Persons Aged 0 Through 6 Years, United States 2010, http://www.cdc.gov/vaccines/recs/schedules/default.htm, Last updated June 15 2010, Accessed on August 4, 2010.

[317] Srinivasan PT, Viraraghavan T, Subramanian KS (1999) Aluminium in drinking water: an overview. W*ater S.A.* **25**, 47-55.