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Original Article

Additive aluminum as a cause of induced immunoexcitoxicity resulting in neurodevelopmental and neurodegenerative disorders: A biochemical, pathophysiological, and pharmacological analysis

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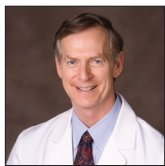
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ABSTRACT

Much has been learned about the neurotoxicity of aluminum over the past several decades in terms of its ability to disrupt cellular function, result in slow accumulation, and the difficulty of its removal from cells. Newer evidence suggests a central pathophysiological mechanism may be responsible for much of the toxicity of aluminum and aluminofluoride compounds on the brain and spinal cord. This mechanism involves activation of the brain's innate immune system, primarily the microglia, astrocytes, and macrophages, with a release of neurotoxic concentrations of excitotoxins and proinflammatory cytokines, chemokines, and immune mediators. Many studies suggest that excitotoxicity plays a significant role in the neurotoxic action of several metals, including aluminum. Recently, researchers have found that while most of the chronic pathology involved in the observed neurodegenerative effects of these metals are secondary to prolonged inflammation, it is the enhancement of excitotoxicity by the immune mediators that are responsible for most of the metal's toxicity. This enhancement occurs through a crosstalk between cytokines and glutamate-related mechanisms. The author coined the name immunoexcitotoxicity to describe this process. This paper reviews the evidence linking immunoexcitotoxicity to aluminum's neurotoxic effects and that a slow accumulation of aluminum may be the cause of neurodevelopmental defects as well as neurodegeneration in the adult.

Keywords: Accumulation in neurons and glia, Aluminofluoride complex, Aluminum, Excitotoxicity, Immunoexcitotoxicity, Microglial activation, Nanoscaled aluminum, Neurodegeneration, Sickness behavior

INTRODUCTION

While aluminum is the third most common metal found in the earth's crust, it has no role to play in normal human physiology, biochemistry, or maintaining health.[36] Humans are exposed to aluminum through several routes, including foods, industrial exposures, agrichemical, geoengineering, drinking water, pharmaceuticals, and vaccines.[39] While absorption from the gut is quite poor, that introduced through parenteral fluids and vaccines is completely absorbed and distributed throughout the body.[112] In addition, there are common food constituents that greatly enhance aluminum absorption from the gut, such as citrate, glutamate, and malate. It may enter through the leaky gut disorder as well. Interestingly, there appears to be a common mechanism

by which aluminum and other known neurotoxic metals (i.e., manganese, mercury, and lead) trigger and propagate their toxic actions within the central nervous system (CNS). This mechanism appears to be immunoexcitotoxicity. This term was coined by the author to link previously described interactions between the immune system and the excitotoxic receptor mechanisms, leading to excitotoxic pathology.[9] The purpose of this review is to discuss the evidence linking immunoexcitotoxicity to aluminum's neurotoxic effects on the CNS, especially neurodevelopment, as regards early exposure and a lifetime of an accumulation from various sources.[43]

BASIS OF ALUMINUM IMMUNOEXCITOXICITY

While aluminum is not recognized as a redox metal, it can induce significant inflammation within various tissues. Redox refers to a variation in the valence of a metal that induces a greater risk of free radical generation, such as with ferric (Fe+3) and ferrous (Fe+2) iron interchange. In chemistry, the loss of electrons makes the metal a free radial, and an excess of electrons makes it an electron donor or antioxidant. Exley explained that while aluminum is a non-redox metal, under certain conditions, it can act as a pro-oxidant.[35] Moreover, aluminum appears to react with the superoxide radical, thus facilitating its destructive potential. Experimental observations also indicate that the formation of superoxide plays a critical step in triggering excitotoxicity-mediated neuronal death through the generation of peroxynitrite.[64]

Aluminum may interfere with the normal biochemistry of cells by a number of mechanisms. One interesting to chronic brain inflammation is the finding that aluminum produces a profound general decrease in nicotine binding involving all brain areas.[44,61] The nicotinic receptor (alpha 7 nicotinic acetylcholine receptor) plays an important role in dampening brain inflammation. Interference with this nicotinic cholinergic neurotransmission can increase brain inflammation.[115] Suppressing this nicotinic receptor allows the aluminum to inflame the tissues by reducing the effects of this anti-inflammatory system. This may be a major mechanism linking aluminum accumulations in the Alzheimer's disease (AD) brain and chronic inflammation that goes beyond the neurotransmitter functions of acetylcholine.

Another way in which aluminum may contribute to neuronal injury, particularly associated with AD, is by interference with calcium homeostasis, which is known to be perturbed in AD and other neurodegenerative disorders.[56,111] For example, aluminum can delay the closure of voltage-dependent calcium channels and block calmodulin (CaM)-dependent Ca2+/Mg2+-ATPase, which is responsible for the extrusion of excess intracellular calcium, one of the protective mechanisms against excitotoxicity.[34,56,97] El-Rahman exposed male albino rats to aluminum sulfate for 35 days by gavage (tube feeding), after which he examined their tissues for

aluminum accumulation.[31] Aluminum accumulation, as well as aluminum-induced neurotoxic effects were observed in a dose-dependent accumulation of aluminum in the examined brain sections of the treated animals. Aluminum-treated rats also showed a marked increase in brain glutamate levels while their gamma-aminobutyric acid (GABA, an inhibitory neurotransmitter) brain levels were decreased, a condition that maximizes excitotoxic damage and is characteristic of immunoexcitotoxicity[31,75,100] [Figures 1 and 2]. The most significant changes in brain tissue included spongiform changes in neurons, especially within the hippocampus, nuclear deformity, and neurofibrillary degeneration, resembling the neurofibrillary tangles in AD.[16] These spongiform microscopic changes are usually indicative of excitotoxicity and not inflammatory changes alone. These changes indicate damage to intracellular neuronal systems by excitotoxicity.

By activating the inflammatory cytokines, especially tumor necrosis factor-alpha (TNF-α), one sees events that can enhance excitotoxicity; in this case, the GABA receptors (an inhibitory neurotransmitter-controlled receptor) are trafficked inside the neuron, thus enhancing excitotoxicity.
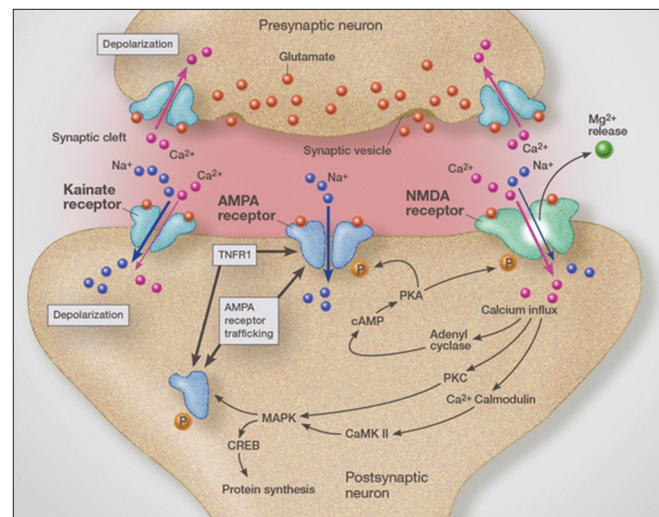

Figure 1: Synaptic illustration showing trafficking of AMPAR initiated by activation of tumor necrosis factor (TNF) R1 by high levels of TNF-alpha, which then releases GluR 2-lacking AMPA receptors from the endoplasmic reticulum. This AMPA type of receptor allows calcium entry into the neuron, thus making it much stronger and potentially more destructive. Internalization of the gamma-aminobutyric acid inhibitory receptor is not shown but occurs when stimulated by inflammation. Na2+: Sodium, Ca2+: Calcium, AMPA:α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, NMDA:N-methyl-D-aspartate,Mg 2+: Magnesium, TNFR: Tumor necrosis factor receptor, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, MAPK: Mitogen-activated protein kinase, CREB: cAMP-response element binding protein, CaMK:Calmodulin-dependent protein kinase, PKC: Protein kinase C.
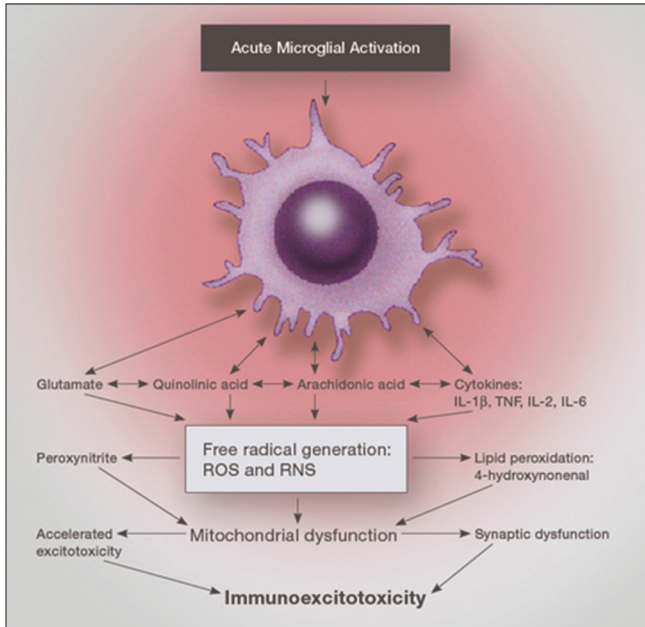
Figure 2: An activated, primed microglial cell initiating both an inflammatory reaction (inflammatory cytokine and inflammatory prostaglandin release) and excitotoxicity (Immunoexcitotoxicity). IL: Interleukin, TNF: Tumor necrosis factor, ROS: Reactive oxygen species, RNS: Reactive nitrogen species.

Other mechanisms also link inflammatory stimulation to excitotoxicity (immunoexcitotoxicity) [Figures 1 and 2].

In another study, Campbell *et al.* observed brain inflammation in animals exposed to aluminum lactate when added to their drinking water.[21] The lowest concentration used in their study (0.01 nM) was equivalent to that associated with AD and aluminum-containing public drinking water. Unlike the above study, they found elevations in nuclear factors kappa B and interleukin-1ß in the brains of the exposed animals but no elevation when exposed to drinking water free of aluminum. Both studies found that systemic exposure to aluminum produced selective inflammation of the brain in selective areas.

It is known that metabotropic glutamate receptor (mGLuR) signaling, as well as that of many other neurotransmitters, is critically dependent on G-protein receptor systems.[71,77] In general, mGluRs (especially group I) enhance excitatory neurotransmission and can, therefore, worsen excitotoxicity.[24] Some are inhibitory of excitotoxicity. Under normal (physiological conditions), they play an important role in long-term potentiation and long-term depression changes, which can induce long-lasting changes in neuronal excitability.[24] High levels of mGluR1 expression are seen in the hippocampus in the face of aluminum exposure, which is proexcitatory.[24] These high levels are induced by aluminum. Mitogen-activated protein kinase/extracellular signal-regulated kinase and mammalian target of rapamycin/p70S6 cell signaling pathways are particularly

important for regulating synaptic plasticity by Group I mGLuRs.[78] Both glutamate and mGluRs play a critical role in brain development.[91,103] Thus, alterations in the patterns of activation of mGLuRs can have a profound effect on eventual brain development and physiology.

By interfering with normal mGLuR function, aluminum and especially aluminofluoride complexes could potentially cause malfunctioning of important brain pathways as well as abnormal architectonic development of the brain.[51] In addition, it is known that aluminum affects glutathione regeneration, which is one of the neuron's main defenses against toxic metals and other toxic influences.[73] Aluminum has also been shown to dramatically lower overall neuronal reduced glutathione levels, with astrocytes being a major source of glutathione for neurons.[73] High levels of glutamate also inhibit glutathione production intracellularly by inhibiting the cystine/glutamate antiporter.[12] In addition, aluminum has been shown to impair gap junctional intercellular communication between astrocytes in culture.[108] In essence, we see an increase in the vulnerability of neurons from an accumulation of aluminum by lowering its primary protective mechanism, glutathione, in a reduced form.

Aluminum can also enhance excitotoxicity by inducing apoptosis of astrocytes, which are thought to be a primary site of aluminum accumulation.[104] Indeed, research evidence shows that, apart from providing trophic support to neurons, astrocytes also play a crucial role in protecting neurons from excitotoxic damage by mediating the clearance of excess glutamate and its storage within the astrocyte.[1] When the astrocytes are dying, this glutamate is released into the extra-neuronal space and becomes excitotoxic.

Aluminum is also known to operate synergistically with other toxic metals, such as copper and iron, to increase brain and spinal cord inflammation.[9] Since the aluminum is not removed, it acts as a constant source of inflammation and enhances the effect of peripheral immune activation (sickness behavior), as one would see with vaccination or re-vaccination. It has been shown that the presence of an inflammatory nidus in the CNS will magnify the pathologic damage to the brain by systemic immune and/or inflammation stimulation.[10]

The inflammatory cytokines are known to act on several enzymes and mechanisms to enhance excitotoxicity.[49] This is especially true of TNF-α. TNF-α, which is elevated with aluminum exposure [Figure 3], is a key cytokine, triggering the release of glutamate from microglia, which occurs by up-regulating glutaminase and gap junction hemichannels.[22,26,107] In addition, this cytokine impairs glutamate uptake, suppresses glutamine synthetase, increases internalization of GABA receptors, and increases GluR2-lacking AMPA receptors.[100,120] In essence, the inflammatory
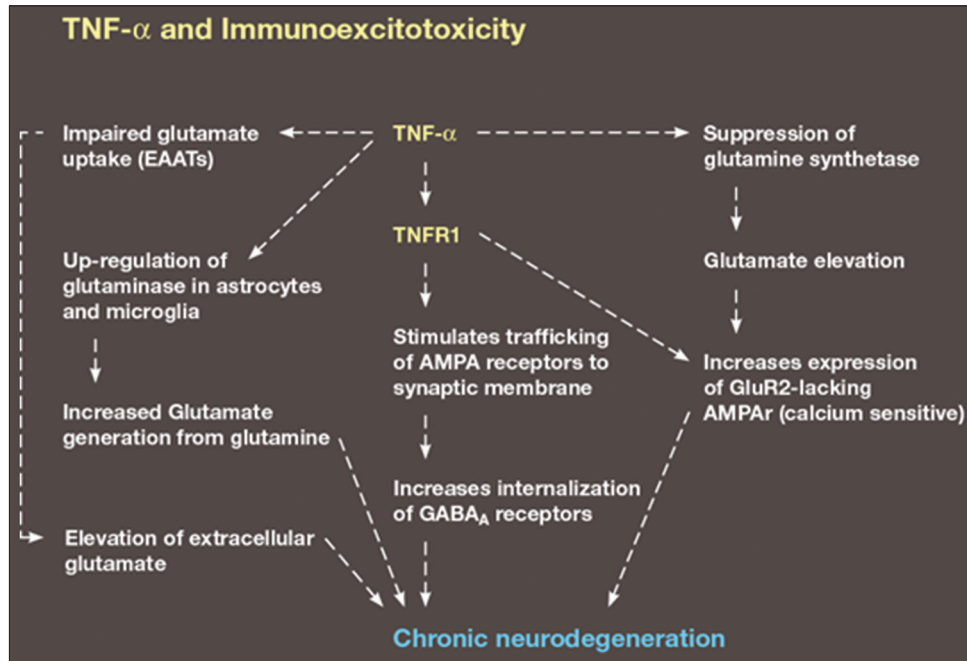
Figure 3: Activation of tumor necrosis factor-alpha mechanisms that enhance excitotoxicity. TNF: Tumor necrosis factor, EAATs: Excitatory amino acid transporters, TNFR: Tumor necrosis factor receptor, GABA: γ-aminobutyric acid, AMPAr: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

cytokines enhance excitotoxicity by inhibiting glutamate uptake into microglia and astrocytes, lowering GABA receptor insertion (an inhibitory transmitter), and increasing trafficking of the gluR2 lacking AMPA receptor into the synaptic membrane (stimulatory). There are two types of AMPA receptors (both fast glutamate receptors)-those that contain the GluR2 subunit and do not increase calcium entry to the neuron and the GluR2-lacking AMPA receptors that will allow calcium entry into the neuron (much like the N-methyl D-aspartate [NMDA] receptor). The latter is much more destructive by excitotoxicity under pathological conditions. This can result in neurodegenerative diseases.

These observations indicate a mechanism by which aluminum can induce immunoexcitotoxicity, a process based on deleterious interactions between inflammatory cytokines (i.e., TNF-α) and excitotoxins (i.e., glutamate). For example, Matyja demonstrated that exposing organotypic cultures of rat hippocampus for 24 h to a combination of aluminum and glutamate, both in subtoxic concentrations, produced typical excitotoxic lesions, which predominantly consisted of mitochondrial abnormalities, both structural and biochemical.[66] Separately, neither aluminum nor glutamate caused neuronal injury.

It has also been shown that aluminum, in combination with other metals (copper and iron), additively increases brain inflammation.[9] Interestingly, much as in the case of aluminum, other neurotoxic metals commonly found in the environment, such as mercury, lead, and manganese, also activate glial cells, promoting inflammation, excitotoxicity, and oxidative stress in the brain.[20,22,70,125] The central biochemical and pathophysiological (biopathological) degenerative effect of all these metals is that they have both an excitotoxic effect and inflammatory effects (biopathological).[9,19,22]

It is important to know what proportion of absorbed aluminum reaches the brain in comparison to other organs. To answer this question, Flarend *et al*. injected New Zealand White rabbits intramuscularly with 26Al radiolabeled aluminum hydroxide and aluminum phosphate and traced their distribution at 28 days post-injection in blood and urine samples as well as tissues by utilizing accelerator mass spectrometry.[38] The Al isotope appeared in the first blood sample at 1 h for both adjuvants, but levels were ×3 higher for the aluminum phosphate than the aluminum hydroxide. Tissue distribution profiles were the same for both compounds (kidney > spleen > liver > heart > lymph nodes > brain). Even though brain levels were low following a single injection, children are receiving multiple injections, each with variable doses of aluminum (most often as either aluminum hydroxide or aluminum phosphate), repeatedly given during early life in addition to a lifetime of aluminum exposure from other environmental sources. In addition, most colleges and universities require attendees to have a new set of childhood vaccines on admission, adding considerably to the total aluminum load. Furthermore, substantial evidence shows that bioavailable aluminum tends to accumulate in the brain over a lifetime.[111,119]

It is of significant concern that low levels alone of environmental aluminum are sufficient to induce neurotoxic outcomes.[21,97] Moreover, experimental evidence shows that aluminum preferentially accumulates in the mitochondria and cell nucleus, which makes this metal very resistant to removal by chelation.[53] The difficulty of removing brain intracellular aluminum will lead to its progressive accumulation over a lifetime, eventually reaching a neurotoxic threshold sufficient to trigger neurodegenerative disease processes.[117] Our exposure to aluminum and nanoaluminum is not decreasing; it is increasing.[16]

We have a combination of *in vitro* and *in vivo* studies that provide indisputable evidence that aluminum can significantly increase the level of proinflammatory cytokines and glutamate (and other excitotoxins) in the CNS.[46,99] Microglia can activate rapidly in response to various disturbances, even peripherally.[29,27,52,82] Once activated, microglia may either assume a reparative/beneficial phenotype (and secrete a number of anti-inflammatory and trophic factors essential for neuronal survival) or behave as a predominantly neurodestructive phenotype. The latter is characterized by the secretion of proinflammatory cytokines, cytotoxic factors, and excitotoxins.[12,15,18] In neurodegenerative diseases such as AD, Parkinson's disease (PD), Huntington's disease (HD), frontotemporal dementia, human immunodeficiency virus dementia, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), activated microglia are present in large numbers, a condition termed microgliosis, strongly implicating these cells in the disease pathology.[15,83]

ALUMINUM AND MITOCHONDRIAL ENERGY PRODUCTION

Aluminum has been shown to interfere with the action of membrane receptors (i.e., G-protein coupled receptors [GPCRs]) cell signaling pathways. It also alters deoxyribonucleic acid integrity and impairs mitochondrial function, all of which will have an enhancing effect on both excitotoxicity in general and, specifically, immunoexcitotoxicity.[2,13,15,60,75,85,101]

Aluminum is known to accumulate in the mitochondria and disrupt several mitochondrial functions, leading to an energy deficit,[16,54,69,88] which by itself may not result in sufficient neuronal dysfunction or damage. However, several studies show that reductions in neuronal energy can dramatically amplify excitotoxic injury.[42,60-62] Impairment of mitochondrial function and energy metabolism by aluminum[58,59,63] would thus be expected to increase the sensitivity of neurons to excitotoxicity and accelerate and potentiate neuronal damage. When energy levels are depressed, even physiological levels of glutamate can be excitotoxic. In addition, when the electron transport chain is impaired, there is an increase in free radical generation, both reactive oxygen species (ROS) and reactive nitrogen species (RNS).[85]

Aluminum is known to concentrate in the mitochondria of neurons, microglia, and astrocytes and reduces energy production.[54,76] Excitotoxicity is significantly enhanced under such conditions, making a direct biochemical link to mitochondrial impairment in neurodegenerative diseases.[2,8,68]

Mitochondria are also responsible for calcium regulation within the cell.[17,20] Dysfunction of this control system can lead to calcium accumulation within the cell and subsequent apoptosis. Calcium is the most abundant cell signaling molecule, and such dysfunctions can lead to many disease states.

Several toxic metals, industrial chemicals, solvents, and some pesticides are associated with mitochondrial dysfunction.[19,22,23] We can see that there is an intimate link between mitochondrial function and neurological health.[58]

Of particular importance is the effect of aluminum on cell signaling pathways, such as G-proteins, phosphatidylinositol-specific phospholipase C, protein kinase C, and calcium homeostasis.[55,64] Strunecka *et al*. has shown that aluminum complexed with fluoride can act as a false activator of GPCRs.[102] Further, she proposes that due to the high affinity of fluoride for aluminum, this complex may occur spontaneously in body fluids.

One should also avoid glutamate, either as added during processing or naturally present, as it is in certain foods. This would include most nuts, beans (especially black beans), red meats, chicken, cheeses, and mushrooms as natural sources of higher glutamate levels. Processes food have very high levels under names either as monosodium glutamate or disguised names, such as hydrolyzed soy, hydrolyzed proteins, natural flavors, autolytic enzymes, protein concentrates, and an evolving number of new names. As stated, this not only increases aluminum levels in the nervous system but also renders the glutamate much more destructive and, in addition, raises brain glutamate levels.[122]

Other aluminum forms, such as aluminosilicates used in tap water, have also been reported in diseased brains (i.e., in the cores of senile plaques in AD patients).[34,118] Furthermore, Evans *et al*., using purified murine microglia exposed to aluminosilicate particles, observed the generation of ROS, indicating microglial activation.[33]

Some of the highest levels of aluminum are found in black tea, and studies have shown that the longer this is brewed, the higher the aluminum level. Tea should not be brewed over 3 min. White tea, the youngest to be harvested, has the lowest

aluminum levels. Tea grown in India has been shown to have the lowest aluminum levels, especially for white tea. Chinese tea has a much higher level. Green teas are intermediate in aluminum levels, also with the lowest level in green tea grown in India. Black tea, high in aluminum, is associated with neurodegenerative diseases. Coffee does not contain high aluminum levels.

Taken together, all the above experimental observations indicate that by promoting oxidative damage and inflammation in the CNS, exacerbating excitotoxic damage by (i) increasing the levels of excitotoxic mediators and (ii) impeding their clearance, aluminum can both trigger and promote neuronal injury. Aluminum-induced microglial/astrocyte-mediated immunoexcitotoxicity combined with its direct neurotoxic effects makes this element a strong candidate for at least enhancing neurodegeneration associated with such disorders as AD, PD, ALS, HD, MS, viral encephalopathies, and chronic traumatic encephalopathy. Notably, all these diseases have been previously linked to over-active glia.[6,7,10,13,80,82]

The excitotoxic cascade can be triggered by an excessive release of glutamate from microglia and/or astrocytes, with elevations in nitric oxide (NO), proinflammatory prostanoids, and generation of a number of ROS/RNS.[11-15] NO elevations triggered by activation of inducible NO synthase increase reactions between NO and superoxide with an associated accumulation of very destructive peroxynitrite.[84] Nitrogen and oxygen species also react with membrane lipids, resulting in the generation of two highly destructive lipid peroxidation products, 4-hydroxynonenal (4-HNE) and acrolein.[47,74] Peroxynitrite, 4-HNE, and acrolein suppress mitochondrial energy production, which dramatically increases the sensitivity to excitotoxicity. Under conditions of reduced energy production, even low levels of glutamate can become excitotoxic.[8,47] It should be noted that glutamate can also activate microglia and enhance cytokine-induced neurodegeneration. Due to this, a self-perpetuating cycle is created in which inflammatory cytokines stimulate the release of glutamate while glutamate, in turn, stimulates the release of inflammatory cytokines. This mutual interaction between inflammatory mediators and the excitatory levels of glutamate further keeps the injured cells locked in a chronic neurodegenerative cycle.[13]

The largest aluminum exposure from vaccines occurs during initial vaccinations soon after birth and during early childhood. Should a child follow the recommended vaccine schedule for the United States, they will receive a total of 5 mg of aluminum by 2 years of age from a total of 17 aluminum-adjuvanted pediatric vaccines.[112] Such repetitive and continuous exposure to aluminum from vaccines could induce prolonged activation of microglia and subsequent release of glutamate and proinflammatory cytokines. Of

special concern is that aluminum in various forms, including adjuvant aluminum, can accumulate in the brain.[25,80,117-119]

AN INTEGRATED HYPOTHESIS OF IMMUNO-EXCITOTOXICITY LINKING ALL OF THIS DATA

The mechanism by which systemic activation of brain microglia occurs is critical to understanding the effect of sequential immune stimulation with immune adjuvants, including aluminum. When microglia are first exposed to a disturbance in homeostasis, they may assume a primed state in which their messenger RNA (mRNA) and membrane receptors are upregulated, but there is no increased release of cytokines, chemokines, interferons or excitotoxins.[113] Subsequent stimulation will activate these primed microglia with a hyper-responsive reaction occurring, leading to several-fold higher concentrations of released proinflammatory cytokines, chemokines and the release of three excitotoxins – glutamate, aspartate, and quinolinic acid (QUIN).[106]

The pathophysiological point of initiation of histological destruction by these toxic substances entails the immune system as the starting point. Involved in immunoexcitotoxicity is the brain's innate immune system, primarily involving microglia, macrophages, and astrocytes. Microglia make up 5–15% of the cells in the CNS cortical grey matter, hippocampus, olfactory telencephalon, and basal ganglion.[32,57,105,109] Under normal conditions, the brain's microglia exist in what has been referred to as a resting or ramified state, even though these cells are far from resting.[15,46,81] In this mode, microglia are constantly extending and retracting pseudopodia, sampling the surrounding microenvironment to assure homeostatic conditions are maintained, in particular, the level of extracellular glutamate. In this ramified state, they can secrete basal levels of neurotrophic substances to maintain connectivity and integrity of synapses and dendrites and actively remove excess glutamate from the extracellular environment, utilizing a series of glutamate transport proteins (EAATs 1–5). Both microglia and astrocytes have this removal system. The astrocyte is the main storage site for glutamate.

The purpose of this review was to describe two mechanisms linking aluminum to neurodegenerative processes and neurological dysfunction – (1) systemic activation of CNS microglia and (2) resulting immunoexcitotoxicity. The first of these mechanisms, referred to as sickness behavior, has been extensively studied and provides both a direct and indirect link between systemic immune activation, activation of CNS microglia, and abnormal neurological symptoms.[28] In an analogous fashion, immune stimulation by aluminum adjuvants has also been shown to result in adverse neurological outcomes through activation of microglia, which are the brain's resident immune cells. Once activated,

microglia become the main source of both proinflammatory immune cytokines and excitotoxins such as glutamate. It is the interaction of cytokines and glutamate receptors that leads to immunoexcitotoxicity. Other than activating glial cells, aluminum also directly impairs a number of energy-related enzymes, promotes brain inflammation and oxidative damage, reduces the levels of brain antioxidants (i.e., glutathione), and disturbs calcium homeostasis. All these effects will amplify immunoexcitotoxic damage. In the immature and developing brain, immunoexcitotoxicity might lead to several neurodevelopmental conditions, such as autism spectrum disorders and seizures. In the mature, and especially the aging brain, these mechanisms can lead to progressive neurodegeneration, as seen with AD, PD, and ALS. It is covered in the book by Dr. Ana Strunecka and me – Cellular and Molecular Biology of Autism Spectrum Disorders.

The surface of microglia contains a number of receptors, including receptors for most of the neurotransmitters, pro- and anti-inflammatory cytokines, chemokines, interferons, and major histocompatibility complex Classes I and II receptors.[15] Microglia also contain characteristic receptors called pattern recognition receptors (PRR), which are constitutively expressed to identify and bind various pathogen-associated molecular pattern sites and other non-self-molecules.[15] In addition, microglia also express toll-like receptors (TLRs), with TLR 1–9 of the 12 of the known TLRs being found on microglia membranes.[116] TLRs not only recognize microbial antigens but also regulate the magnitude and duration of the immune response. Recognition of various ligands by the PRR can initiate the generation and release of superoxide through *the* activation of nicotinamide adenine dinucleotide phosphate oxidase.[64] The generated superoxide can then react with NO to form the highly destructive radical peroxynitrite.[46,84] Due to the expression of these numerous immune markers, microglia are often referred to as the nervous system's resident immune cells.[82]

There is also evidence that systemically administered aluminum from drinking water can specifically activate TNF-α without activating other cytokines. For example, Tsunoda and Sharma exposed male BALB/c mice to aluminum sulfate-containing drinking water ad libitum at concentrations of 0, 5, 25, and 125 ppm aluminum for 1 month and found significant expression of TNF-α mRNA in the cerebral cortex.[114] Elevations in this cytokine followed a dose-dependent response. The source of the TNF-α was likely from activated microglia. Importantly, these changes occurred at aluminum concentrations commonly encountered in public drinking water. Thus, the study by Tsunoda and Sharma indicates that even very small amounts of aluminum can activate microglia in a pro-inflammatory mode.

There is growing evidence that both glutamate and immune cytokines play crucial roles in various aspects of brain development.[40,65,103] Furthermore, the architectonic development of the nervous system is carefully controlled by a programmed rise and fall of brain glutamate levels and receptor activation during development.[40,65] Perturbations of glutamate and cytokine levels by aluminum early in life could thus be extremely detrimental to normal brain development.

There is suggestive evidence that microglia can become stuck in a neurodestructive mode over long periods.[15,79,82,124] Rather than chronic activation, it may be that the repeated stimulation of primed microglia leads to chronic, progressive neurodegeneration. The presence of aluminum deposits within the neurons and glial cells could act as a continuous stimulus for immunoexcitotoxicity. There is now sufficient evidence from a great number of studies to call for a re-evaluation of the use of aluminum additives for human consumption or as immune adjuvants.

Two forms of aluminum are of special concern: Aluminum-L-glutamate and nanoscaled aluminum, both of which have high absorption from the gut and passage into the brain, as well as higher toxicity profiles than aluminum alone. Adding to this concern is the fact that glutamate, both as a food additive and naturally occurring in foods, is common in the Western diet. Deloncle *et al.* injected Al-L-glutamate subcutaneously and i.v. for 5 weeks and demonstrated a significant increase in aluminum content in several areas of the animal's brain, including the hippocampus, occipitoparietal cortex, cerebellum, and striatum.[30] It is of considerable interest that 50% of the animals given subcutaneous injections of aluminum glutamate developed neurological disturbances such as trembling, equilibrium disturbances, and convulsions, leading to death. This is suggestive of an excitotoxic effect. Supporting this conclusion, Deloncle *et al.* found significant elevations in glutamate in the occipitoparietal cortex of Al-L-glutamate-treated animals.[30] These observations suggest that the Al-L-glutamate complex can cross the blood-brain barrier (BBB).

We must keep in mind that when it rains, the nano aluminum sprayed in the air is deposited in the groundwater, lakes, rivers, and streams. As a result, all plants will now have a higher aluminum level.

When assessing aluminum's potential toxicity, one must also consider absorption and distribution. While absorption from foods is considered to be quite small, under certain conditions, this can be increased substantially. For example, organic acids and some amino acids increase aluminum absorption significantly. Increasing absorption is as follows: Aluminum citrate > aluminum tartrate > aluminum gluconate > aluminum lactate > aluminum glutamate > aluminum chloride, aluminium sulfate, and aluminum nitrate.[26]

When considering immunoexcitotoxicity, one is concerned with two events regulated by activated microglia: (i) proinflammatory cytokine/chemokine release and (ii) release of excitatory amino acids, particularly glutamate, quinolinic acid and aspartate – all excitotoxins. It is the excitotoxicity component rather than inflammation alone that appears to be the main pathological mechanism for actual damage to neurons and their processes. For example, research shows that even exposure to high concentrations of TNF-alone for 24 hours a day for 6 days does not result in neuronal death.[124,127] In contrast, lipopolysaccharide (LPS) or TNF-stimulation of macrophages induces robust neurotoxicity, which is completely inhibited by the NMDA receptor antagonist MK-801.[124] Both the glutaminase inhibitor 6-diazo-5-oxo-l-norleucine and the gap junction inhibitor carbenoxolone also inhibited LPS/TNF-α-induced neurotoxicity by effectively suppressing glutamate production by activated macrophages.[124] Altogether, these observations suggest that inflammation alone is not necessarily sufficient for brain injury, but rather it is the combination of inflammatory cytokines/chemokines and excitotoxins (e.g., glutamate and quinolinic acid) that are most injurious, in other words, immunoexcitotoxicity.

Of particular interest is the observation by Suarez-Fernandez *et al.* that chronic aluminum exposure in mixed cultures of astrocytes and neurons results in significant astroglial apoptosis and associated neuronal loss.[104] Given that neurons are dependent on astrocytes for homeostatic control and antioxidant protection and that astrocytes play a critical role in regulating extracellular levels and transport of glutamate, one would not be surprised at this neurotoxic interrelationship. That excitotoxicity secondary to a release of glutamate from the dying astrocytes is the main neurotoxic mechanism is suggested by the observation that neuronal death occurred in cultures containing approximately 10% astrocytes but not in near-pure neuronal cultures containing only 1% astrocytes.[104] Dying astrocytes also release other microglial activators such as purines and ATP.[3]

NATURAL PLANT EXTRACTS THAT REMOVE AND/OR NEUTRALIZE ALUMINUM TOXICITY IN CELLS

Fortunately, there are several natural products that can either chelate and remove aluminum from biological systems or render it non-toxic without its removal. One of the most impressive is curcumin.[7,87] Due to its poor absorption from the gut, nanosized forms have been developed that increase absorption over 40-fold. Once in the blood, curcumin is easily and widely biodistributed and passes the BBB easily, entering the CNS.

Curcumin can improve the mechanisms within the mitochondria, such as improved biogenesis and fusion, reduce the accumulation of beta-amyloid toxicity, reduce its inflammatory effects, and, thereby, in the process, improve synaptic activity and its functional proteins.[87] In addition, curcumin has shown protective effects against alpha-synuclein, the misfolded protein characteristic of PD.[59,123]

Naringin, a plant flavonoid, has been shown to prevent memory impairment and mitochondrial oxidative damage in aluminium-exposed rats.[86] Aluminium-induced caspase activation and neuroinflammation have also been attenuated by hesperidin in rats.[50] Carnosine has also been shown to enhance mitochondrial function in the face of ischemia and neurodegeneration.[4,6] It also attenuates the overactivation of autophagia. While carnosine is eventually destroyed by the enzyme carnosinase in the blood, acetyl-L-carnosine is not and can persist much longer. Both forms of carnosine are available as supplements. Other natural compounds that mainly protect against aluminum toxicity in tissues include rosemary extract, oregano oil, resveratrol, quercetin, propolis, apigenin, and royal jelly.[5,45,48,96,63]

It has also been shown that the probiotic Lactobacillus plantarum CCFM639 also significantly protects multiple organs, including the brain, from damage by aluminum and lowered significantly aluminum levels.[126] Most are quite safe and have few or no side effects. Several, such as nano-curcumin, also reduce iron toxicity by preventing iron absorption as well as toxicity within tissues. Triphala will also remove fluoride.[98] One should never squeeze a lemon in their tap water or tea, as this drastically increases aluminum absorption. Lemon water made with filtered water or distilled water is safe.

A SLOW ACCUMULATION OF ALUMINUM OVER A LIFETIME

Most people, even many physicians, assume that toxins are dangerous in high acute doses. As a result, many ignore the aspect of a slow progressive accumulation in tissues and cells. We now know that aluminum accumulates slowly and that low levels can eventually reach toxic levels.[89,92,121] This is especially of concern in the CNS, as it naturally contains fewer antioxidant enzymes, has a high dependence on mitochondrial energy production, and is very vulnerable to immunoexcitoxicity induced by systemic as well as CNS inflammation.[33,89,90,92,110,113]

Of special concern are injections of vaccines containing aluminum adjuvants, as 100% of this aluminum is absorbed, unlike that taken orally. The toxicity also depends on the person's size and weight. Infants and small children are much more vulnerable than adults based on these considerations.[94,95,112]

Yet, even in adults, one can gradually accumulate enough aluminum in the CNS, its neurons and glia to eventually result in neurodegeneration as one ages. Aluminum appears to be very difficult to remove from the cells and can persist and gradually accumulate at high enough levels to result in neurodegeneration and CNS disease.[37] Transport of the injected aluminum appears to travel to the CNS via macrophages.[25,67]

It has been noted that more younger people are getting ALS than in the past, which was at that time considered a disease of the older person. It has been shown that the aluminum burden from the present vaccine schedule for youths, including babies as young as 6 months of age, has reached levels far higher than that deemed safe for adult oral consumption, which is only partially absorbed. It has been shown that systemic macrophages rapidly consume injected aluminum from the adjuvants and is carried to the CNS (Macrophages are very difficult to distinguish from native microglia and have similar functions in the CNS).[25,41]

While the vaccine schedule has now been expanded so that the average child will receive over 40 injections before starting school, which means the child is getting a very high dose of aluminum rather rapidly, as the accumulative dose is the sum of the individually added adjuvants. A significant amount of this aluminum is stored in the brain and spinal cord glia and neurons. Many pediatricians will give as many as 6–9 injections on a single office visit.

With adults getting yearly influenza vaccines and a number of other vaccines, such as the hepatitis B vaccine, tetanus vaccines, the shingle vaccine, and the pneumococcal vaccines, to say nothing of the very high level of aluminum in the Gardasil vaccines, one is not surprised that we are seeing the high degree of illness and especially neurodegenerative disease, in our population.[62,72]

What concerns me is that these children are receiving a dose of neurotoxic aluminum that is also being deposited in their spinal cord, especially the motor cells. These cells have a high energy requirement and are thus susceptible to being highly sensitive to excitotoxicity triggered by the aluminum in the neuron as well as the surrounding glia.

Dr. Chris Shaw is the head of neuroscience in Vancouver and an expert in research concerned with autism spectrum disorders and ALS. I asked him how often he saw microglial activation in his studies on aluminum and ALS. He responded, "Always."[93,94] We are now seeing ALS occurring at a much younger age, yet it also occurs in the older age groups as before. I am convinced that the aluminum from the grossly expanded vaccine schedule is responsible for this horrifying disease's appearance in the younger population.

With people getting an influenza injection each year, as well as other highly recommended vaccines, we are also seeing a significant rise in all neurodegenerative diseases over the past decade. To most of the medical profession, this is a mystery. We are also seeing a rise in the use of pesticides and herbicides, which, in addition, make a major contribution to the rise in neurodegenerative diseases. We must think in terms of toxin synergy.

CONCLUSION

Aluminum is a major neurotoxin mainly triggering immunoexcitoxicity. During a person's lifetime, the concentration of aluminum slowly builds from oral absorption from food stuffs [incomplete], inhalation from the atmosphere, and drinking tap water. In addition, injected aluminum as found in many vaccine adjuvants in the childhood vaccine schedule contain aluminum that is 100% absorbed. The early exposure to this toxic metal can also interfere with the proper neurodevelopment of the nervous system, both by activating the inflammatory pathways and excitotoxicity chronically [immunoexcitotoxicity] during this critical period that is rather intense over the first several years of life.

As a person ages, not only are the neurons and glia undergoing pathophysiological assaults by aluminum, both from such vaccine adjuvants and that absorbed from food and water, which accumulate over a lifetime, resulting in sensitive cells and subcellular organelles receiving a pathophysiological dose within these critical neural cells and structures.

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