Aluminum, Alzheimer’s disease (AD) and autism spectrum disorder (ASD)

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Complex relationships and multifactorial etiology lead to heterogeneous and variable phenotypes in ASD

Lauren Matelski and Judy Van de Water, Risk factors in autism: Thinking outside the brain, Journal of Autoimmunity, 67 (2016) 1-7

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Lukiw WJ, Alexandrov PN, Grigorenko AI, Andreeva TV, Rogaei EI, Bhattacharjee S, Clement C, Zhao Y, Jones BM, Sethi-Dua P, Li YY, Cui CG, Sambamurti K, Percy ME, Pogue AI
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Autism One Meeting – Chicago IL USA
25-29 May 2016

Topics to be covered in this lecture

- aluminum is abundant in our environment
- aluminum is implicated in autism spectrum disorders (ASD)
- aluminum is implicated in Alzheimer’s disease (AD)
- aluminum is attracted to the genetic material in the nucleus
- aluminum binds to biological phosphates, induces reactive oxygen species (ROS) and activates the ‘activator’ transcription factor NF-κB
- NF-κB up-regulated micro RNA (miRNA) and down-regulates many messenger RNAs (mRNAs) and hence gene expression
- aluminum, TREM2 and amyloidogenesis (the buildup of amyloid in the central nervous system, CNS)
- aluminum enters the brain through the circulation (vasculature)
- mobilization of aluminum into the biosphere

Earth’s Crust

<table>
<thead>
<tr>
<th>Element</th>
<th>Approximate % by weight</th>
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<tr>
<td>Oxygen</td>
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<tr>
<td>Silicon</td>
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<tr>
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<td>Iron</td>
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<td>Sodium</td>
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<tr>
<td>Potassium</td>
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<tr>
<td>Magnesium</td>
<td>2.1</td>
</tr>
<tr>
<td>All others</td>
<td>1.5</td>
</tr>
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</table>

Common Elements Important in Living Organisms

<table>
<thead>
<tr>
<th>Element</th>
<th>Percent in Earth/Percent in Human Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>0.01% (trace)</td>
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<tr>
<td>Hydrogen</td>
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<tr>
<td>Helium</td>
<td>0.0% (trace)</td>
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<tr>
<td>Carbon</td>
<td>0.2% (trace)</td>
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<tr>
<td>Nitrogen</td>
<td>0.002%</td>
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<tr>
<td>Oxygen</td>
<td>0.003%</td>
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<td>Sodium</td>
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<td>Potassium</td>
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<tr>
<td>Magnesium</td>
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<tr>
<td>Sulfur</td>
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<tr>
<td>Chlorine</td>
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<tr>
<td>Calcium</td>
<td>0.002%</td>
</tr>
<tr>
<td>Iron</td>
<td>0.002%</td>
</tr>
</tbody>
</table>

Other major sources of Aluminum

Food, water, beverages, medicines, vaccines, dust, industrial and mining exposure
Earth’s Crust

Element Approximate % by weight
Oxygen 46.6
Silicon 27.7
Aluminum 8.1
Iron 5.0
Calcium 3.6
Sodium 2.8
Potassium 2.6
Magnesium 2.1
All others 1.5

Other major sources of Aluminum
Food, water, beverages, medicines, vaccines, dust, industrial and mining exposure

Common Elements Important in Living Organisms

Element Percent in Earth/Percent in Human Body
Hydrogen 0.14/9.5
Helium Trace/Trace
Carbon 0.03/1.5
Nitrogen Trace/3.3
Oxygen 47/65
Sodium 2.8/0.2
Magnesium 2.1/0.1
Calcium 3.6/1.5

ABILITY OF METAL SULFATES TO INTERACT WITH BIOMOLECULES

[nanomolar concentrations; physiologically relevant]

Aluminum is an extremely high charge density cation

Ionic charge 3+
Ionic radius 0.05 nm
Ionic Z²/r = 18

Al >>>>>Fe >> Zn >> Cu >>>> Mg

22 May 2015

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- mobilization of aluminum into the biosphere

ADDITIONAL EVIDENCE THAT ALUMINUM IS INVOLVED IN NEUROLOGICAL DISEASES OF THE BRAIN (AD) AND RETINA (AMD)


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EVOLVING CONCEPTS OF HUMAN BRAIN FUNCTION
(100 years ago; on the 24 hr clock system of human evolution, humans have studied brain structure and function for less than 1 second)

Notable contemporaries: Camillo Golgi 1844-1926; Maxime Bichowsky 1845-1928; Sigmund Freud 1856-1939; Santiago Ramon y Cajal 1852-1934; Korbinian Brodman 1868-1918.

Both the human association neocortex and the retina are composed of multiple cellular layers each with different, complimentary, highly interactive functions:

- Association neocortex - control
  ~1 square foot of neocortex
- Human retina - control
  ~1 square inch of retina

Both AD and AMD are highly focused disruptions of the association neocortex and the retina.
Early Moderate Severe
AD Progression

DISTORTED CYTOARCHITECTURE AND LOSS OF NEURITES/SYNAPTIC CONTACTS HAVE THE STRONGEST CORRELATION WITH AD PROGRESSION

NISSL/GOLGI - SILVER STAINING
RABBIT BRAIN CONTROL
RABBIT BRAIN Al3+ treated

Lukiw WJ, McLachlan DRC (1985) unpublished

Aluminum is implicated in Alzheimer’s disease (AD); N=9 major reasons
- aluminum increased in AD brain (active regions)
- aluminum affects the same messenger RNAs (mRNAs) as in AD
- aluminum affects the same microRNAs (miRNAs) as in AD
- aluminum recapitulates inflammatory signaling and changes in the innate-immune responses as is seen in AD
- aluminum induces reactive oxygen species (ROS) and activates the ‘activator’ transcription factor NF-κB as is seen in AD
- aluminum induces amyloidogenesis as is seen in AD
- aluminum up-regulates proinflammatory genes and down-regulates brain essential genes (i.e. synaptic proteins) as is seen in AD
- aluminum in drinking water increases AD risk
- chelators that remove aluminum from the brain improves the outlook for AD patients

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The ability of aluminum to compact chromatin from active euchromatin to inactive heterochromatin is second to none; an important biological function for aluminum.


Aluminum analysis (X-ray fluorescence microscopy; XFM) of human brain nuclei using high brilliance X-ray beamline XFM-2-ID-E of the Advanced Photon Source (APS); 1.4 km diameter ring; US Department of Energy, Argonne National Laboratory, University of Chicago; 0.1-0.4 μm beam diameter, 10 KeV; raster scan of 3x3 mm silicon nitride windows; using an energy dispersive germanium detector (Ultra-LegE, Canberra Instruments, Meriden CT); ~4 million separate analyses of 16 elements in a 4-day experiment.

CONCLUSION - aluminum highly enriched in heterochromatin; virtually absent from euchromatin.


Conclusions for this section
- aluminum is involved in chromatin compaction;
- the ability of aluminum to compact chromatin from active euchromatin to inactive heterochromatin is second to none;
- an important biological function for aluminum is to modulate the state of compaction of chromatin and hence the global regulation of gene expression;
- non-homeostatic aluminum-mediated compaction of euchromatin to heterochromatin is an important pathological effect of aluminum in eukaryotic brain cells.


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Gene Expression – the process by which DNA signals are converted into functional proteins: the first step is ‘transcription’

Aluminum crosslinking of chromosomal protein and DNA

Ability of metal sulfates to repress gene transcription by RNA polymerase II (RNAP II)
[nanomolar concentrations; physiologically relevant]

[Al+Fe] > Al >> Fe > Zn > Cu >>>> Mg

Ability of metal sulfates to repress gene transcription by RNA polymerase II
[nanomolar concentrations; physiologically relevant]

As in AD, ~66% of all transcripts down-regulated (repression) and ~33% of all transcripts up-regulated (activation) a feature common to metal ion toxicity (Al + Fe) and Alzheimer’s disease. This appears to involve differential gene regulation mechanisms.

Essential components of the human neurovascular unit (NVU)

The highly vascularized human brain contains about 430 km of 5 μM diameter cerebrovascular (cerebral microvessels) tubes that supply the brain with oxygen, glucose and other nutriment support.
HUMAN PRIMARY BRAIN CELL MODELS

HNG  HAG  HMG  hBMEC

A: human neuronal-glial cell co-culture  B: human astroglial cells  C: human microglial cells  D: human brain microvascular endothelial cells

INDUCTION OF ROS IN HUMAN NEURONAL-GLIAL CELLS

ROS-sensitive green fluorescent reporter (λ<sub>max</sub>=525 nm) such as H<sub>2</sub>DCFDA (Molecular Probes-Invitrogen, Carlsbad, CA)

STRESSED BY HYPOXIA, IL-1β, β-PEPTIDES, NEUROTOXIC METAL (Al<sub>3+</sub>)

CONTROL  STRESSED

METAL-INDUCED OXIDATIVE STRESS IN HUMAN NEURAL CELLS – ROS ASSAY

Gene expression profiling of Alzheimer's disease neocortex and hippocampus (mRNA)


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STUDIES OF HUMAN BRAIN mRNA COMPLEXITY

Messenger RNA ANALYSIS

- A HIGHLY LABILE, TRANSLATOR MOLECULE (HALF-LIVES IN MINUTES-HOURS)
- TRANSMITS ESSENTIAL GENETIC INFORMATION FROM DNA TO PROTEIN
- RNA POPULATIONS ARE A REFLECTION OF THE PHYSIOLOGICAL STATUS OF THE CELL (HEALTH, DISEASE, STRESS, DEVELOPMENT, AGING)

Tuesday 27 February 2007

CENTRAL DOGMA OF MOLECULAR BIOLOGY

DNA → RNA → PROTEIN

Friday 22 May 2015

years               minutes, hours                 years
(12,000 yr)           (1 min to 12 hr)             (10,000 yr)

GENETICS-EPIGENETICS OF ALZHEIMER’S DISEASE (AD) AND AGE-RELATED MACULAR DEGENERATION (AMD)

micro RNA ↑
messenger RNA ↓

(miRNA↑, mRNA↓)

**up-regulation of specific micro RNA (miRNA), and down-regulation of messenger RNA (mRNA) complexity appears to be a very active genetic process in the aging human brain and retina**


miRNA – GENETIC MECHANISM

~27,000 mRNAs, ~2000 miRNAs

Friday 22 May 2015
Transgenic animal models of Alzheimer's disease (Tg-AD)
TREM2 COX-2 COX-1 PS1 cPLA2

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miRNA-34a and TREM2

miRNA-34a
TREM2 messenger RNA ↓
2 AD CASES – and 1 case of Balints syndrome (brain and retina in the same specimen available; all females)

- Balints syndrome (88 yr old female) – AD that moves posteriorly in the brain - damage in the temporal lobe-occipital lobe circuits – inflammatory degeneration and amyloid pathology in the limbic system, primary visual cortex (PVC) and retina

- advanced AD – amyloid inflammatory degeneration and amyloid pathology in the limbic system, primary visual cortex (PVC) and retina

- advanced AD inflammatory degeneration and amyloid pathology in the limbic system, primary visual cortex (PVC), thalamus (LGN) and retina

- TREM2 expression down in the temporal lobe neocortex and retina

Conclusion: in all 3 AD/Balints syndrome cases where the eye and brain were both available at autopsy, the entire neocortical-PVC-LGN-retinal axis showed signs of inflammatory degeneration, amyloid pathology and TREM2 deficits.

Pathologists: Drs J. Deck and DRC McLachlan, University of Toronto

Brain neocortex and retinal TREM2 – data from the same brain

Control (79.4 yr AD1 = 78.9 yr; AD2 = 81.1 yr; all females Caucasian; the diagnosis of AD was both pre- and post-mortem confirmed - family history, genotyping (BACE1, PSEN1); ApoE4, CDR, MMSE; SP and NFT counts had no significant difference; no significant differences in brain weight, PMI <2.1 hrs; TREM2 decreased in both brain and retina

Deck JD, McLachlan DRC, Lukiw WJ, unpublished 2015
Aluminum contributes to amyloidogenesis: (i) by aggregating amyloid monomers into higher order structures; (ii) while triggering an NF-kB-miRNA-34a mediated down-regulation of TREM2 and the ability to sense and clear amyloid.


Stressors
- Aβ42
- IL-1β
- TNFα
- hypoxia
- UV
- aluminum

ROS → NF-kB → miRNA-9, miRNA-34a, miRNA-125b, miRNA-146a, miRNA-155

Stressors
- Aβ42
- IL-1β
- Th1a
- hypoxia
- UV
- aluminum

Disrupted miRNA-mRNA signaling in Alzheimer’s disease (AD)
- miRNA-mRNA signals in
  - aging human and AD brain
  - stressed mouse and human brain cells (neuronal, astroglial, microglial, endothelial)
  - SxFAD (amyloid over-expressing) brain and retina
  - age-related macular degeneration (AMD)
  - human prion disease (CJD, GSS)

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How does aluminum access the neuronal nuclei of the brain neocortex and hippocampus?

- pathways through the systemic circulation
  - one existing study in human arteries

The brain is very highly vascularized; 2,000 km of blood vessels in the average adult human brain; blood volume: 5 liters, circulates through the brain once every 1-1.5 minutes; \[SV \times HR \times \text{minutes} = BV; \text{time} = \frac{BV}{SV \times HR}; \text{time} = \frac{5\text{L}}{(60\text{ml/s})} = 1 - 1.5 \text{ minutes}; \text{brain receives first blood from the cardiopulmonary circulation that is 20-25\% of the total.}

Cerebral circulation

Studies in Human Blood Vessels

- excise blood vessels from 1 hr post-mortem interval (PMI) brains or brain biopsy
- perfuse vessels with ultrapure saline
- ash in platinum vessels, heat and hydrolyze with ultrapure nitric acid
- analyze for trace metals using inductively coupled plasma emission (ICPE) or electrothermal atomic absorption (EAA)
- only Mg, Hg and Al levels were investigated further
aluminum (sulfate) affinity for various cell types (in culture)

- hepatocyte (1 +/- 1 ug/g)
- microglial (human) (1.5 +/- 1.5 ug/g)
- astroglial (rat) (2.5 +/- 1.5 ug/g)
- astroglial (human) (6.1 +/- 2 ug/g)
- endothelial (HUVEC) (11 +/- 5 ug/g)
- endothelial (hBMEC) (36 +/- 8 ug/g)
- neuron (rat, interneuron) (15 +/- 5 ug/g)
- neuron (human, interneuron) (58 +/- 12 ug/g)
- neuron (pyramidal) (104 +/- 18 ug/g; 10-25x)

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Nuclear energy will power world’s largest aluminum smelter; now being built in Russia’s Saratov region, complete with two 950 MW pressurized water reactors linked to a 2.3 million tons per year aluminum smelter; RUSAL—12% world aluminum production; www-world-nuclear-news.org; www-rusal.ru

- It takes about 2 tons of alumina and 17000 kWhr of electricity to produce 1 ton of pure aluminum
- This facility alone will produce 525,000 pounds per hour; 3750 pounds per minute; 146 pounds per second; 24/7
- Fiber reinforced aluminum (FRA), a mixture of carbon fiber and aluminum, is the most recent advance in aluminum structural products

\[
\text{Nuclear fission: } \text{U-235} + n \rightarrow \text{Ba-141} + \text{Kr-92} + 3n + 170 \text{ MeV}
\]

Mobilization of aluminum into the biosphere

- In the last 60 minutes our civilization has produced another ~6,100 tons (12,200,000 pounds) of 99.9% pure aluminum
- together our laboratories in the US, Canada and Russia have shown that very much less than 1/100 billionth of that amount is extremely genotoxic to human brain and CNS gene structure and function


Conclusions-1

- aluminum is ubiquitous in our diet and our environment;
- aluminum is involved in chromatin compaction; the ability of aluminum to compact chromatin from active euchromatin to inactive heterochromatin is second to none;
- a biological function for aluminum may be to compact chromatin (DNA plus protein) into higher order structures; in diseases such as AD this system may get out of control and down-regulate the expression of many brain essential genes.


Conclusions-2

- many aspects of aluminum treated primary brain cells and/or transgenic animals (5xFAD) recapitulate what is seen in AD, and especially in aged AD patients;
- specific vascular cell types (i.e endothelial cells) serving the human brain may act as a conduit to attract and accumulate aluminum in specific regions of the brain;
- the basilar arteries, middle cerebral artery (MCA) and the posterior cerebral artery (PCA) which serves the hippocampus contain the highest values of Al in both post-mortem tissues and in aluminum-treated hBMEC cells;

Conclusions-3

- molecular carriers for aluminum in the blood, serum and other blood components require further investigation; the role of aluminum transport and aluminum carriers in the systemic circulation is not well understood;
- aluminum interactions with neurobiology is exceedingly complex and more research needs to be undertaken to further clarify its role in the aging CNS;
- the continuing mobilization of aluminum into the environment is of serious and continuing healthcare concern

Conclusions

- aluminum has an important function in selective chromatin compaction;
- pathological amounts of aluminum probably shift normally euchromatic gene regions into dense, inactive heterochromatin regions;
- an important biological function for aluminum is the global regulation of gene expression;
- aluminum promotes amyloidogenesis and senile plaque formation by at least two interdependent mechanisms: directly, by inducing Aβ42 peptide aggregation, and indirectly, by a mRNA-34a-mediated inhibition of TREM2 and the ability of natural TREM-2-mediated Aβ42 clearance mechanisms

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ACKNOWLEDGEMENTS

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National Disease Research Interchange, Philadelphia PA, USA
Netherlands Brain Research Institute, Amsterdam, NETHERLANDS
New York State Institute for Basic Research, Staten Island NY, USA
Oregon Health Sciences University, Portland OR, USA
Southern Eye Bank, Metairie LA, USA
University of California, Irvine CA, USA
University of Kentucky Alzheimer’s disease Brain Bank, Lexington KY, USA
University of Maryland Brain and Tissue Bank, Baltimore MD, USA
University of Massachusetts, Worcester MA, USA
University of Pennsylvania School of Medicine, Philadelphia PA, USA
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