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Aluminum toxicity and astrocyte dysfunction: A metabolic link to neurological disorders

Joseph Lemire, Vasu D. Appanna *

Department of Chemistry and Biochemistry, Laurentian University, Sudbury, Ontario, Canada P3E 2C6

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ABSTRACT

Aluminum (Al) has been implicated in a variety of neurological diseases. However, the molecular mechanisms that enable Al to be involved in these disorders have yet to be fully delineated. Using astrocytes as a model of the cerebral cellular system, we have uncovered the biochemical networks that are affected by Al toxicity. In this review, we reveal how the inhibitory influence of Al on ATP production and on mitochondrial functions help generate globular astrocytes that are fat producing machines. These biological events may be the contributing factors to Al-triggered brain disorders.

Introductory comments

Al is the most abundant metal in the Earth's crust, but has remained mostly isolated from biological systems due to its lack of availability. Three features have recently come into play that have made Al more bioavailable 1) An increase in anthropogenic acidification of soils, 2) the increased utilization of the metal for industrial purposes, and 3) its utilization as a flocculent in water treatment [1–3]. This enhanced bioavailability has resulted in the accumulation of the metal in living organisms including humans. The skeletal system, the liver, and the brain are some of the primary sites where Al deposits have been observed [4–6]. Diseases such as encephalopathy, Alzheimer's, Parkinson's, and osteomalacia have been associated with the presence of this metal [7–10].

The molecular targets of Al toxicity are multifaceted and appear to involve the disruption of essential metal homeostasis such as calcium (Ca), magnesium (Mg), and iron (Fe) [1,5,11]. Al has been demonstrated to replace Ca within the bone and interferes with Ca-based signaling events [1,5,12]. Mg has been observed to be replaced by Al for binding to phosphate groups on the cell membrane, on ATP, and on DNA [13–15]. Perhaps the main target of Al toxicity is Fe dependent biological processes. Al's interference with Fe homeostasis also leads to the production of ROS [16,17]. The perturbation of Fe homeostasis and the subsequent generation of ROS both contribute to its toxicological effects [11,17] (Fig. 1).

The connection between Al and neurological disorders has eluded researchers for many years. Although progress has been made in this regard, the link between Al and neurological disorders such as Alzheimer's and Parkinson's diseases has yet to be precisely delineated. The discovery of Al in the brain of Alzheimer's patients and the association of Al with amyloid plaques have provided some evidence to the connection between the metal toxin and Alzheimer's disease [18–20]. The involvement of Al in the induction and phosphorylation of Tau protein, as well as the promotion of neuroinflammatory transcripts has been demonstrated [10,21–25].

One key player of the functioning brain that has not been fully studied in the relation to Al toxicity are the astrocytes. Astrocytes participate in a variety of critical roles including, scaffolding (structural support), metabolic support, neurotransmitter homeostasis, and lipid metabolism within the brain [26,27]. It is plausible then that any insult imposed upon the astroglia would result in neurological dysfunction. Al and ROS alike have been demonstrated to affect the workings of astrocytes [28–32]. Here, we review our research on how Al disturbs the biochemical interactions of the astrocyte. We have uncovered the drastic diminution of aerobic energy production and the abnormal mitochondrial metabolism in astrocytic cells exposed to Al. This Al-induced disruption of energy results in the inability of the actin cytoskeleton to polymerize, thus causing the loss of cellular morphology. The Al-treated astrocytes are globular compared to the dendritic structures evident in the control cells [33]. In addition, the Al-induced disruption of mitochondrial enzymes is reflected in diminished β-oxidation of fatty acids and enhanced production of lipids. Indeed, Al-stressed astrocytes are replete with fat deposits [34].

* Corresponding author. Tel.: +1 705 675 1151 2112; fax: +1 705 675 4844.
E-mail address: vappanna@laurentian.ca (V.D. Appanna).

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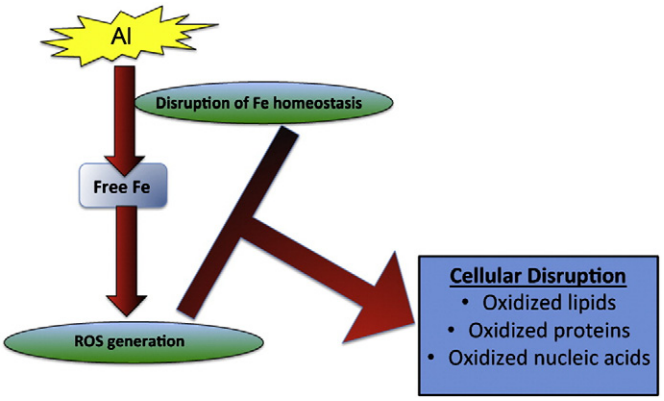

Fig. 1. Al toxicity leads to defective Fe homeostasis and oxidative stress. Free Fe within the cell produces ROS through Fenton chemistry. ROS then interferes with numerous cellular constituents including lipids, protein, and nucleic acids.

Al-induced energy depletion

Perhaps the main feature of Al-toxicity that poses the biggest threat to astrocytes is the inability of these cells to synthesize ATP via oxidative phosphorylation. Oxidative metabolism is heavily reliant on Fe to execute the combustion of citric acid [35,36]. Enzymes of the tricarboxcylic acid (TCA) cycle such as aconitase (ACN) [EC 4.2.1.3 – aconitate hydratase], succinate dehydrogenase (SDH) [EC 1.3.5.1 – succinate dehydrogenase (ubiquinone)] and fumarase (FUM)[EC 4.2.1.2 – fumarate hydratase] contain Fe–S clusters [36]. SDH is also a bridge to the electron transport chain (ETC), where it functions as Complex II. The ETC also contains other Fe dependent enzymes such as, Complex I [EC 1.6.5.3 — NADH dehydrogenase (ubiquinone)], Complex III [EC 1.10.2.2 — ubiquinol–cytochrome–c reductase], and Complex IV [EC 1.9.3.1 — cytochrome-c oxidase] [36]. It then stands to reason that if Fe homeostasis was to be affected under Al-insult, oxidative ATP production would be severely compromised.

We initially observed a defect in oxidative metabolism within the soil microbe, *Pseudomonas fluorescens*. Indeed, the activity and expression of Fe-dependent ACN was decreased under Al-toxicity [37]. Similar observations were made with SDH, Complex I, and Complex IV [38]. This resulted in a loss of NADH and subsequently a diminution of ATP production in an aerobic fashion [39]. Similarly, when hepatocytes were treated with Al, Fe dependent enzymes such as SDH, Complex IV, and FUM were also inhibited [40,41]. This effect led to a decrease in the production of NADH and ATP [41]. Due to the inability of the TCA cycle to consume citrate, the HepG2 cells were transformed into lipid factories that produced and stored fatty acids [42]. Another consequence of the Al toxicity was the switch to an anaerobic life style [43]. Al has been demonstrated to induce ROS [34]. ROS has also been shown to promote an anaerobic state within the cell [43,44]. HepG2 cells exposed to Al accumulate α-ketoglutarate (KG), a known antioxidant, by the downregulation of α-ketoglutarate dehydrogenase (KGDH) [40]. This KG reacts with ROS to produce succinate [45]. Succinate accumulates due to the diminished expression of SDH. This accumulation of succinate under Al-toxicity, promotes anaerobiosis by a prolyl-hydroxylase (PHD) and hypoxia inducible factor-1α (HIF-1α) dependent manner [43]. Hence, a metabolic link between Al, ROS, and ATP production does exist.

Diminished ATP production in astrocytes will have a major impact within the brain, as energy is intimately linked to functional neurophysiology [26,46]. We have indeed demonstrated that an astrocytic cell line exposed to varying concentrations of Al and ROS experienced a sharp decrease in ATP synthesis [33,34]. Like *P. fluorescens* and HepG2 cells, Fe dependent enzymes are severely affected. The Fe-reliant enzymes of the TCA cycle SDH, FUM, and ACN undergo a reduction in activity and expression in Al-treated astrocytes (personal observation). Other enzymes of the TCA cycle, like the NAD dependent ICDH (NAD-ICDH) [EC 1.1.1.41 — isocitrate dehydrogenase (NAD)] and KGDH [EC 1.2.4.2 — oxoglutarate dehydrogenase (succinyl-transferring)] were also inhibited and the Complexes I and IV experienced a similar fate in Al and ROS treated astroglia [33,34]. This perturbation of key Fe-dependent enzymes resulted in marked diminution in ATP formation [33] (Fig. 2).

Ineffective energy production via oxidative phosphorylation and mitochondrial dysfunction have been suggested to be the root cause of neurological disorders [47,48]. We have recently demonstrated that treatment of astrocytic cells with Al (an inducer of ROS) leads to dysfunctional mitochondria and a loss of energy synthesis [33,34]. This disruption in the ability of astrocytes subjected to Al to produce energy may limit the participation of the glial cells in their cognate neurophysiological tasks. Indeed, this may have major implications on the structure of the astrocytes.

Al toxicity elicits morphological changes

One key feature of astrocytes is their interaction with neurons through their philopodia (end-feet) [26]. The actin cytoskeleton is essential in maintaining the morphological features of the astrocytes, a pivotal component of its function [49]. This characteristic is a crucial molecular mediator of brain scaffolding and nutrient exchange [50]. ATP is essential in the turnover of the actin cytoskeleton [51]. As discussed previously, marked reduction in ATP production under Al-stressed conditions has been observed [33,34]. We have additionally shown how this impacts on the loss of cellular morphology in Al-treated astrocytes [33]. Al-treated astrocytic cells are globular compared to more stellate-like features evident in the control cells (Fig. 3) [33]. The modulation of cell morphology by Al toxicity has also been reported in neurons [52] and plant cells [53]. It appears that the cytoskeleton is also sensitive to ROS [54,55] and cadmium [56], toxins that may have similar impact on cellular morphology.

It is important to note that the toxicological effect of the Al on the cytoskeleton was not triggered by the reduction in the expression of actin, but was rather caused by the inability of the actin to form a

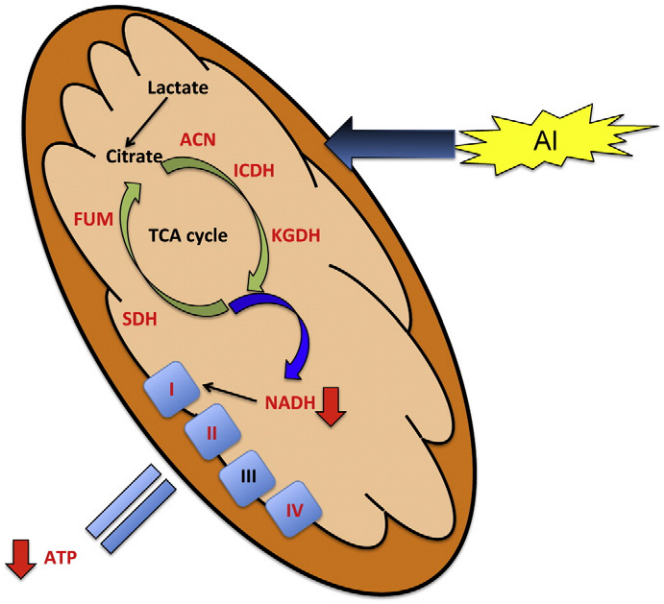

Fig. 2. Al inhibits oxidative energy production. Al perturbs Fe dependent enzymes of the TCA cycle ACN, FUM, and SDH. NADH producing enzymes such as ICDH and KGDH are also inhibited. This leads to a loss in NADH production. Al also impedes ETC enzymes such as Complex I, II, and IV. The loss of NADH production and inhibition of the ETC results in a loss of mitochondrial ATP production. Red = decrease in levels. (ACN = aconitase, ICDH = isocitrate dehydrogenase, SDH = succinate dehydrogenase, KGDH = α-ketoglutarate dehydrogenase, FUM = fumarase).

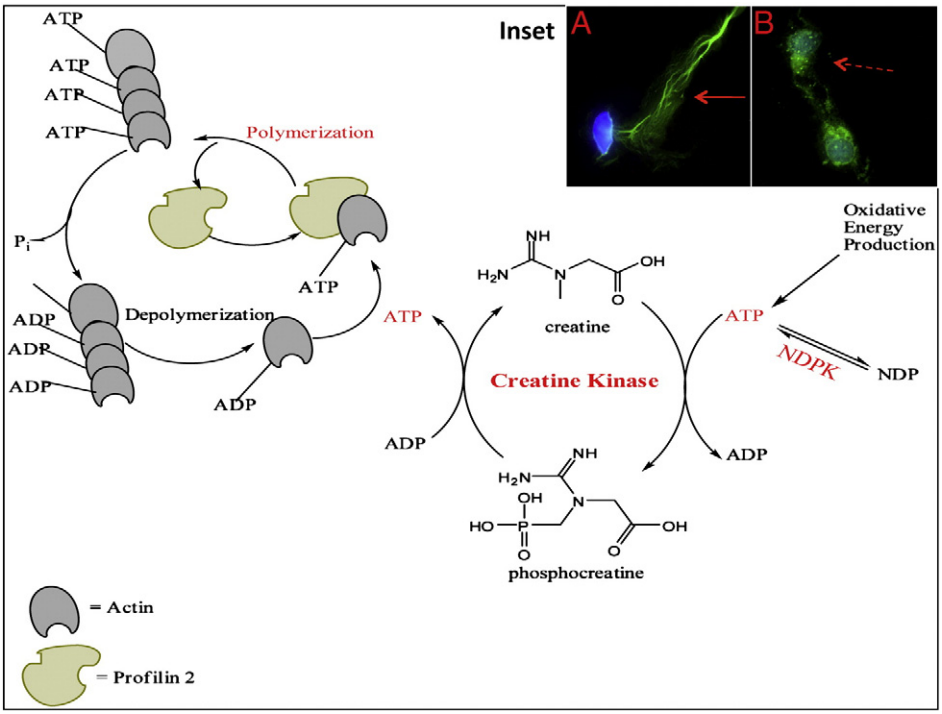

Fig. 3. A molecular pathway that promotes globular astrocytic cells during Al toxicity. The decreased levels of ATP production via oxidative phosphorylation and ineffective ATP buffering are major contributing factors. The levels of energy buffers such as phosphocreatine and NTP, as well as the enzymes that produce them, CK and NDPK respectively, also decrease under Al stress. Red = decrease in levels. (NDPK = nucleotide diphosphate kinase, NDP = nucleotide diphosphate) Inset: Astrocytoma stained with Hoestch (nucleus = blue) and FITC-Phalloidin (actin = green). A) Control B) 0.1 mM Al treatment. Microscopy was performed at 60X ocular objective. Figure adapted from J. Lemire et al. 2009. (Note the globular astrocytes in the stressed conditions).

filamentous cytoskeleton [33]. Actin levels were similar in both control and Al-stressed cells [33]. This phenomenon appears to be directly connected to the lack of ATP available to polymerize the actin. Creatine kinase (CK) [EC 2.7.3.2 - creatine kinase] and nucleoside diphosphate kinase (NDPK) [EC 2.7.4.6 - nucleoside-diphosphate kinase], enzymes involved in the buffering of high energy phosphates, were also downregulated in activity and expression under Al stress [33]. CK has been demonstrated to provide local energy for the actin polymerization [57,58]. The loss of ATP production coupled with the inhibition of CK under Al stress are the two important contributing factors that impede the polymerization of actin [33]. Al also lowers the levels of profilin-2 in these astrocytoma cells; this moiety is pivotal in the rapid polymerization of actin [33]. Hence, the combination of defective ATP production and the decrease in the expression of profilin-2 work in tandem to give Al-treated astrocytic cells a globular feature, an attribute that may lead to astrocyte cellular dysfunction (Fig. 3). A loss of functional astrocytes is a contributing factor in neurological disorders.

Lipid metabolism and Al stress

The dysfunctional TCA cycle provoked by Al treatment has other major biological implications than just the loss of energy production. The inability of the TCA cycle to metabolize citric acid leads to a rerouting of organic acids to alternative metabolic networks. The astrocytes are forced to funnel metabolites and various carbon sources towards lipid production when challenged by Al and ROS [34]. Similar observations are also evident in HepG2 cells. When fed citrate, glucose, fructose, or lactate, Al stressed cells switch to a lipogenic metabolism and become fat-producing machines [42]. In astrocytes and hepatocytes alike, lipid-producing pathways are enhanced, while the capacity to burn the lipids is reduced [34,42]. Al toxicity thus appears to mimic conditions that evoke obesity.

Since the TCA cycle is altered under Al stress, citrate is instead metabolized by citrate lyase (CL) [EC 2.3.3.8 — ATP citrate synthase] and subsequently acetyl-CoA carboxylase (ACC)[EC 6.4.1.2 — acetyl-CoA carboxylase] [34]. The latter generates malonyl-CoA, a metabolite that condemns the cell to produce fat [59]. The upregulation of CL and ACC mediates the accumulation of lipids [34]. Furthermore, the oxidative environment generated by Al toxicity compels the cell to pool KG in an effort to combat ROS [34]. This ketoacid neutralizes ROS with the concomitant formation of succinate, a moiety known to signal anaerobiosis [43,45]. However, the channelling of KG for anti-oxidative defense, limits its utilization in L-carnitine synthesis [60]. L-carnitine is a moiety that is essential to transport lipid moieties into the mitochondria for β-oxidation [60]. Levels of L-carnitine and the enzymes {butyrobetainealdehyde dehydrogenase (BBADH) [EC 1.2.1.8 — betaine-aldehyde dehydrogenase] and butyrobetaine dioxygenase (BBDOX)[EC 1.14.11.1 — gamma-butyrobetaine dioxygenase]}, involved in its synthesis were also found to be sharply diminished in Al stressed conditions [34]. Although the connection between L-carnitine synthesis, Al toxicity, and KG has yet to be precisely unravelled, it is within reason to suggest that these molecular insights provide a plausible pathway to lipogenicity in Al-challenged astrocytes [34]. Due to the lack of L-carnitine, the lipids were unable to be burned. This was evident in the accumulation of lipid visualized within the cell (Fig. 4) [34].

In hepatocytes, this overproduction coupled with the inability to consume lipids, may be a link between Al toxicity and obesity [42]. Astrocytes contribute to lipid production in the brain [61–64]. Thus, an Al-induced disruption of lipid metabolism within the astrocytes would lead to a general defective cerebral lipid profile. Indeed, altered lipid metabolism in the brain is often observed during numerous neurological disorders [65,66]. Additionally, L-carnitine has been demonstrated to have a functional role in stabilizing membranes, modulating genes, and enhancing cholinergic neurotransmission within the brain [67]. Our observed alteration in L-carnitine and

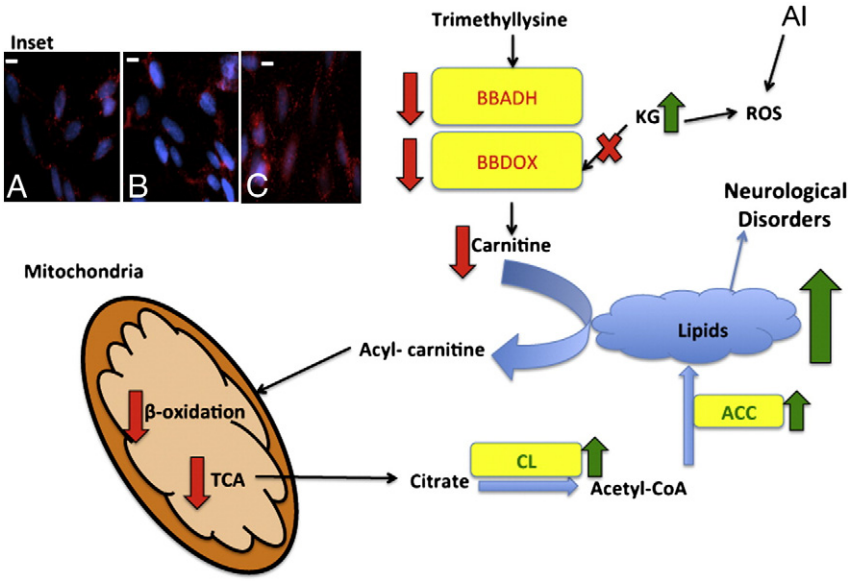

Fig. 4. Al toxicity, L-carnitine biosynthesis and lipid accumulation. Al decreases the activity of the enzymes, BBADH and BBDOX, involved in the synthesis of L-carnitine, a moiety necessary for the translocation of lipids into the mitochondria for β-oxidation. KG, a necessary cofactor for BBDOX is instead shuttled toward ROS detoxification. In addition Al inhibits the TCA cycle. This leads to a diminished capacity of the mitochondria to oxidize lipids. Citrate is instead shipped to the cytoplasm where CL and ACC commit it to lipid production. Both CL and ACC are promoted by Al toxicity. This metabolic shift renders the astrocytes into fat-factories. Red = decrease in levels, green = increase in levels. (BBADH = butyrobetainealdehyde dehydrogenase, BBDOX = butyrobetaine dioxygenase, CL = citrate lyase, and ACC = acetyl-CoA carboxylase). Inset: Astrocytoma stained with Hoestch (nucleus = blue) and oil red-O (lipids = red). A) Control B) 0.01 mM Al treatment and c) 0.1 mM Al treatment. Microscopy was performed at 40X ocular objective. Figure adapted from J. Lemire et al. 2011.

lipid metabolism in Al-treated astrocytes indeed helps establish a molecular link between Al and lipid-mediated neurological disorders (Fig. 4).

Concluding remarks

Al toxicity is a multifaceted stressor, affecting a variety of biological functions. Al interferes with Fe metabolism, an event that mediates the intracellular formation of ROS [16]. Fe is an essential cofactor for many enzymes and key to the operation of oxidative metabolism. Lack of Fe and increased levels of ROS both interfere with oxidative energy production [42,68]. Thus, Al toxicity alters the TCA cycle and inhibits oxidative energy production. This dearth of ATP production within the brain may be an important cause for neurological disorders, as the brain is an energy intensive organ. However, this disruption in primary metabolism extends to the inability of the cytoskeleton to contribute to proper astrocytic morphology. This perturbation in the morphology of the astrocytes will have an impact on the brain as astrocytes provide the scaffold and regulate the blood-brain barrier through their end-feet [26]. The dysfunctional mitochondrial metabolism also leads to an increase in lipid production and the inability to oxidize lipids. This accumulation of lipids and the inability to consume them may also contribute to neurological disease states. Taken together the lack of energy production, the loss of cellular morphology, and the altered lipid metabolism are all hallmarks linking Al to astrocytic dysfunction, a process that may manifest into neurological diseases (Fig. 5). Although these molecular findings have been uncovered in this cellular model, they provide interesting cues to the neurotoxicity of Al in-vivo.

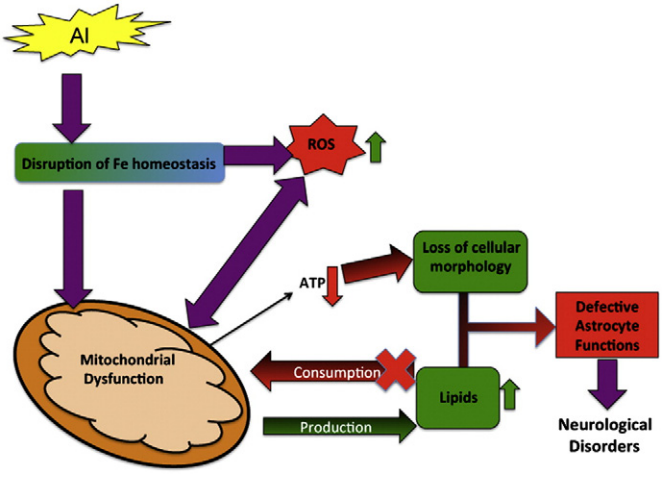

Fig. 5. A global view of Al toxicity in astrocytes. Al creates ROS through the interference with Fe homeostasis. The defective Fe homeostasis and the ensuing ROS production render the mitochondria dysfunctional. The Al-stressed mitochondria are unable to produce energy and consume lipids. This leads to a loss in cellular morphology and a tendency to accumulate lipid respectively. These factors contribute to the inability of the astrocyte to perform its natural functions within the brain. Red arrows = decrease in levels, green arrows = increase in levels.

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References

[1] M. Kawahara, T. Nagata, Y. Sadakane, Biomed. Res. Trace Elem. 18 (2007) 211–220.
[2] M. Gomez, J.L. Esparza, M. Cabre, T. Garcia, J.L. Domingo, Toxicology 249 (2008) 214–219.
[3] C. Exley, Trends Biochem. Sci. 34 (2009) 589–593.
[4] H.O. Hellstrom, K. Michaelsson, H. Mallmin, B. Mjoberg, Age Ageing 37 (2008) 217–220.
[5] C. Exley, Aluminum and Alzheimer's Disease: The Science that Describes the Link, Elsevier Science, Amsterdamn, The Netherlands, 2001.
[6] Z.X. Xu, L. Fox, S. Melethil, L. Winberg, M. Badr, J. Pharmacol. Exp. Ther. 254 (1990) 301–305.
[7] M.V. Peto, Rejuvenation Res. 13 (2010) 589–598.

[8] E.H. Jeffery, K. Abreo, E. Burgess, J. Cannata, J.L. Greger, J. Toxicol. Environ. Health 48 (1996) 649–665.
[9] J.A. Jaffe, C. Liftman, J.D. Glickman, Am. J. Kidney Dis. 46 (2005) 316–319.
[10] S.C. Bondy, Neurotoxicology 31 (2010) 575–581.
[11] Z. Wu, Y. Du, H. Xue, Y. Wu, B. Zhou, Neurobiol. Aging (2010).
[12] C.M. Nday, B.D. Drever, T. Salifoglou, B. Platt, J. Inorg. Biochem. 104 (2010) 919–927.
[13] C. Exley, J.D. Birchall, J. Theor. Biol. 159 (1992) 83–98.
[14] W.R. Harris, G. Berthon, J.P. Day, C. Exley, T.P. Flaten, W.F. Forbes, T. Kiss, C. Orvig, P.F. Zatta, J. Toxicol. Environ. Health 48 (1996) 543–568.
[15] M. Kawahara, M. Kato-Negishi, Int. J. Alzheimers Dis. 2011 (2011) 276393.
[16] C. Exley, Free Radic. Biol. Med. 36 (2004) 380–387.
[17] S.C. Bondy, S. Kirstein, Mol. Chem. Neuropathol. 27 (1996) 185–194.
[18] C. Exley, Subcell. Biochem. 38 (2005) 225–234.
[19] C. Exley, M.M. Esiri, J. Neurol. Neurosurg. Psychiatry 77 (2006) 877–879.
[20] S.V. Verstraeten, L. Aimo, P.I. Oteiza, Arch. Toxicol. 82 (2008) 789–802.
[21] R.W. Shin, T.P. Kruck, H. Murayama, T. Kitamoto, Brain Res. 961 (2003) 139–146.
[22] R.W. Shin, V.M. Lee, J.Q. Trojanowski, J. Neurosci. 14 (1994) 7221–7233.
[23] P.N. Alexandrov, Y. Zhao, A.I. Pogue, M.A. Tarr, T.P. Kruck, M.E. Percy, J.G. Cui, W.J. Lukiw, J. Alzheimers Dis. 8 (2005) 117–127 discussion 209–115.
[24] W.J. Lukiw, M.E. Percy, T.P. Kruck, J. Inorg. Biochem. 99 (2005) 1895–1898.
[25] S.P. Guy, D. Jones, D.M. Mann, R.F. Itzhaki, Neurosci. Lett. 121 (1991) 166–168.
[26] N.J. Maragakis, J.D. Rothstein, Nat. Clin. Pract. Neurol. 2 (2006) 679–689.
[27] M. Michikawa, Q.W. Fan, I. Isobe, K. Yanagisawa, J. Neurochem. 74 (2000) 1008–1016.
[28] J.B. Sass, L.C. Ang, B.H. Juurlink, Brain Res. 621 (1993) 207–214.
[29] G.W. Guo, Y.X. Liang, Brain Res. 888 (2001) 221–226.
[30] C. Struys-Ponsar, O. Guillard, P. van den Bosch de Aguilar, Exp. Neurol. 163 (2000) 157–164.
[31] O. Sorg, T.F. Horn, N. Yu, D.L. Gruol, F.E. Bloom, Mol. Med. 3 (1997) 431–440.
[32] S.D. Rao, H.Z. Yin, J.H. Weiss, J. Neurosci. 23 (2003) 2627–2633.
[33] J. Lemire, R. Mailloux, S. Puiseux-Dao, V.D. Appanna, J. Neurosci. Res. 87 (2009) 1474–1483.
[34] J. Lemire, R. Mailloux, R. Darwich, C. Auger, V.D. Appanna, Toxicol. Lett. (2011).
[35] M.W. Hentze, M.U. Muckenthaler, N.C. Andrews, Cell 117 (2004) 285–297.
[36] M. Ristow, Curr. Opin. Clin. Nutr. Metab. Care 9 (2006) 339–345.
[37] J. Middaugh, R. Hamel, G. Jean-Baptiste, R. Beriault, D. Chenier, V.D. Appanna, J. Biol. Chem. 280 (2005) 3159–3165.
[38] J. Lemire, R. Mailloux, C. Auger, D. Whalen, V.D. Appanna, Environ. Microbiol. 12 (2010) 1384–1390.
[39] R. Singh, J. Lemire, R.J. Mailloux, D. Chenier, R. Hamel, V.D. Appanna, PLoS One 4 (2009) e7344.
[40] R.J. Mailloux, R. Beriault, J. Lemire, R. Singh, D.R. Chenier, R.D. Hamel, V.D. Appanna, PLoS One 2 (2007) e690.
[41] R.J. Mailloux, R. Hamel, V.D. Appanna, J. Biochem. Mol. Toxicol. 20 (2006) 198–208.
[42] R. Mailloux, J. Lemire, V. Appanna, Cell. Physiol. Biochem. 20 (2007) 627–638.
[43] R.J. Mailloux, V.D. Appanna, Toxicol. In Vitro 21 (2007) 16–24.
[44] R.J. Mailloux, S. Puiseux-Dao, V.D. Appanna, Biochimie 91 (2009) 408–415.
[45] N.I. Fedotcheva, A.P. Sokolov, M.N. Kondrashova, Free Radic. Biol. Med. 41 (2006) 56–64.
[46] C. Verderio, M. Matteoli, Brain Res. Rev. 66 (2011) 106–114.
[47] P.J. Adhihetty, M.F. Beal, Neuromolecular Med. 10 (2008) 275–290.
[48] M.P. Mattson, M. Gleichmann, A. Cheng, Neuron 60 (2008) 748–766.
[49] V. Perez, T. Bouschet, C. Fernandez, J. Bockaert, L. Journot, Eur. J. Neurosci. 21 (2005) 26–32.
[50] N.J. Abbott, L. Ronnback, E. Hansson, Nat. Rev. Neurosci. 7 (2006) 41–53.
[51] H.Y. Kueh, T.J. Mitchison, Science 325 (2009) 960–963.
[52] T.B. Shea, E. Wheeler, C. Jung, Mol. Chem. Neuropathol. 32 (1997) 17–39.
[53] M. Amenos, I. Corrales, C. Poschenrieder, P. Illes, F. Baluska, J. Barcelo, Plant Cell Physiol. 50 (2009) 528–540.
[54] I. Sponne, A. Fifre, B. Drouet, C. Klein, V. Koziel, M. Pincon-Raymond, J.L. Olivier, J. Chambaz, T. Pillot, J. Biol. Chem. 278 (2003) 3437–3445.
[55] I. Dalle-Donne, R. Rossi, A. Milzani, P. Di Simplicio, R. Colombo, Free Radic. Biol. Med. 31 (2001) 1624–1632.
[56] Y. Liu, D.M. Templeton, Can. J. Physiol. Pharmacol. 88 (2010) 341–352.
[57] V.B. Mahajan, K.S. Pai, A. Lau, D.D. Cunningham, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 12062–12067.
[58] J.W. Kuiper, H. Pluk, F. Oerlemans, F.N. van Leeuwen, F. de Lange, J. Fransen, B. Wieringa, PLoS Biol. 6 (2008) e51.
[59] M.J. Wolfgang, M.D. Lane, J. Biol. Chem. 281 (2006) 37265–37269.
[60] F.M. Vaz, R.J. Wanders, Biochem. J. 361 (2002) 417–429.
[61] J. Edmond, Can. J. Physiol. Pharmacol. 70 Suppl (1992) S118–S129.
[62] N. Bernoud, L. Fenart, C. Benistant, J.F. Pageaux, M.P. Dehouck, P. Moliere, M. Lagarde, R. Cecchelli, J. Lecerf, J. Lipid Res. 39 (1998) 1816–1824.
[63] J.J. Volpe, J.C. Marasa, J. Neurochem. 25 (1975) 333–340.
[64] M. Lopes-Cardozo, O.M. Larsson, A. Schousboe, J. Neurochem. 46 (1986) 773–778.
[65] R.M. Adibhatla, J.F. Hatcher, Subcell. Biochem. 49 (2008) 241–268.
[66] A.A. Farooqui, Neuroscientist 15 (2009) 392–407.
[67] L.L. Jones, D.A. McDonald, P.R. Borum, Prog. Lipid Res. 49 (2010) 61–75.
[68] S. Levi, E. Rovida, Biochim. Biophys. Acta 1790 (2009) 629–636.