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Metal toxicity and neuroinflammation

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Abstract

Acute inflammation can represent an effective immune response to the corporeal presence of organisms of exogenous origin or damaged cells of intrinsic origin, both of which are potentially injurious. Very often, such inflammation persists long after the triggering stimulus no longer poses a threat. Such a chronic condition can ultimately be more harmful than the original triggering agent. The means by which metallic compounds can provoke undesirable and extended inflammatory changes within the nervous system are diverse. This short review classifies the likely mechanisms underlying their toxicity by taking into account their known chemical properties and also by reflecting on other injurious events that commonly occur together with inflammation. The brevity of this survey does not allow focusing exhaustively on each individual metal but rather seeks to uncover some intracellular susceptible biochemical loci, based on the chemistry of each class of metals. Developmental and senescence-related characteristics are considered as these stages of life often involve especial vulnerabilities. Another feature addressed is that while research is generally conducted on purified and well-defined agents, exposures in the real world generally involve diverse mixtures in which the individual toxicity of a component can be enhanced or suppressed by the presence of other chemicals.

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Neuroinflammation, Neurotoxic metals, Inflammation, Oxidative stress, Glia.

Introduction

Various metals can initiate inflammatory events within nervous tissue, and these are likely to involve several different mechanisms and can be arranged in groups based on consideration of their elemental and chemical properties. Inflammatory events are often closely associated with redox-related changes and an increased rate of production of reactive oxygen species (ROS). The most potent of these such as the hydroxyl radical (OH.) are extremely short lived and thus can attack nearby molecules only [1]. Other oxidant species such as the superoxide anion (O_2.') and hydrogen peroxide have much lower reactivity, and they need to be converted to more reactive species before they can act as oxidants. However, this enables them to diffuse from their site of origin and act at more distant sites. The causal relation of inflammatory and oxidant events is often difficult to determine as it can be bidirectional in that inflammatory cell species can produce ROS while free radical—triggered processes can activate inflammatory immune responses. In the case of some classes of metal, their known ability to catalyze ROS production is likely to be the initial event leading to inflammation. The scope of this review is to arrange metal elements into sets built around a common chemistry, which are likely to share a means of promoting both oxidant and inflammatory processes, thereby accounting for much of their toxicity. This general outline is emphasized rather than assembling a compendium of all known toxic metals.

Other initiators of neuro-inflammation are nanoparticulate and colloidal materials with a large surface area can lead to the superficial binding and partial sequestration of a variety of metal salts [2]. This can result in complex interactive processes involving the particles themselves and their partially chelated superficial constituents. The intricacy of effects wrought by more heterogeneous materials such as colloids and nanoparticles will also be discussed.

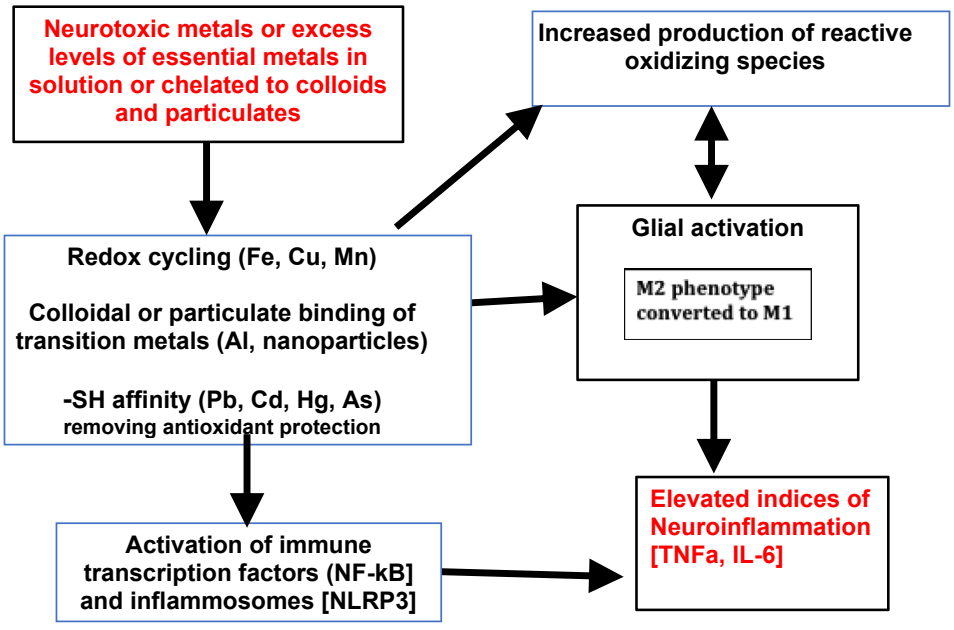
The general areas of the report that are covered are illustrated in Figure 1.

Classes of metal involved in neuro-inflammation

Metals that can undergo valence change under biological conditions (Fe, Cu, Mn)

In addition to their potential toxicity, these transition metals are all essential for life. The potential of Fe2+ and Cu2+ for flux of valence allows them to act within a Fenton reaction and thus enable the production of the

Figure 1



Trajectories by which both neurotoxic metals and excessive levels of essential transition metals can promote chronic neuroinflammation.

highly reactive hydroxyl radical for hydrogen peroxide which can be produced by mitochondrial respiration [3]. The hazardous nature of these metal salts has led to evolution of several protein species able to tightly chelate them and keep their cytosolic ionic concentrations very low.

Iron and copper

Increased levels of iron in specific brain regions are associated with a wide range of neurodegenerative diseases including Parkinson's disease, Alzheimer's disease (AD), and Huntington's disease [4]. Evidence for a degree of causality between these correlations include the finding that cognitive deficits and neuroinflammation induced by lipopolysaccharide are alleviated by administration of deferoxamine, a powerful Fe chelator [5]. Similarly, Fe2+ can heighten the inflammatory state in activated microglia [6]. Disruption of iron homeostasis through brain hemorrhage results in gliosis and elevated levels of inflammatory cytokines. Iron accumulation in microglia after central nervous system damage leads to their transition toward the M1 inflammatory phenotype [7]. Both Fe and Cu bind to amyloid peptide Ab with high affinity leading to its aggregation to form cellular inclusions, which results in elevated neuroinflammation [7]. The valency of intracellular copper may be a major determinant of whether it is beneficial or neurotoxic. Cu2+ exacerbates the inflammatory response produced by Ab while Cu+ effects polarization of cells from an anabolic anti-inflammatory M2 configuration to a proinflammatory M1 phenotype [8]. However, the Cu binding protein ceruloplasmin is effective in inhibiting both the Cu and Fe-catalyzed Fenton reaction [9].

Manganese

The properties of Mn salts differ markedly from those of Fe and Cu salts. Mn2+ is a stable ion, not readily oxidized to the trivalent state and thus not readily able to generate ROS by the Fenton reaction. Thus, redox bioenergetics of Mn are uncharacteristic of transition metals [10]. Nevertheless, Mn neurotoxicity is accompanied by microglial activation leading to production of TNF-α and IL-1β and neuroinflammation and consequent neuronal apoptosis [11,12]. Mn-induced microglial activation can lead to inflammatory responses in astroglia by way of NF-κB-enabled increases in mRNA levels of inflammatory cytokines [13].

Metals with an affinity for sulfhydryl groups

Lead, cadmium, mercury, and tin

These are all environmentally prevalent neurotoxic heavy metals with no known essential role in organisms. Their ability to form covalent bonds is especially relevant in that they will attach to sulfhydryl groups, thereby both reducing the major source of reducing power in the cell (glutathione) and inactivating many enzymes possessing sulfur atoms at their active sites.

Cadmium and mercury are able to induce production of protective metallothionein proteins, around 30% of whose amino acid residues consist of cysteine. This enables the sequestration of these metals, thereby reducing the toxic potential. However, overexpression of metallothionein-1 in a genetic mouse model of AD only modestly reduced evidence of inflammation around amyloid plaques [14].

Mercury

Hg can be neurotoxic in its elemental, inorganic, and organic forms. The neurodevelopmental abnormalities associated with exposure to methylmercury are well known after the major tragic episode at Minamata Bay. Methylmercury exposure is associated with neuroinflammation and upregulation of expression levels of mRNAs for many inflammatory cytokines, and a close association with oxidant events is indicated by the protective effects of N-acetyl-L-cysteine [15]. Ionic Hg salts do not rapidly penetrate the blood-brain barrier, and their toxicity is primarily expressed as renotoxicity. However, extended exposure of rats to low levels of HgCl2 can cause neuronal and glial death in the motor cortex without evidence of inflammation [16]. The immune and inflammatory changes seen in patients with AD resemble those found after exposure to Hg, and it has been proposed that Hg may contribute to the development of AD [17].

It is possible that the neurotoxicity of all forms of Hg may have an underlying commonality. Elemental Hg, having crossed into the brain, is thought to form mercuric salts which cannot readily cross out of the brain. As metallic Hg is very inert, this may account for neurotoxic event after Hg inhalation. Likewise, organic Hg compounds, having entered the brain, also become gradually converted to ionic mercury which can get trapped inside the blood-brain barrier [18]. This slow conversion may account for the extended time (4 months) that a scientist inadvertently exposed to an acute lethal dose of dimethylmercury in a single incident did not express any symptoms whatsoever [19]. It is possible that the ultimate neurotoxicant in all types of mercury poisoning may be inorganic mercury.

Lead

Intermittent exposure to low levels of lead beginning at infancy can lead to neuroinflammation, gliosis, and neuronal loss [20]. Several studies have reported that developmental lead exposure contributes to the later appearance of hallmarks of features associated with AD such as Aβ accumulation, tau pathology, and inflammation [7]. A variety of epigenetic changes relating neonatal Pb exposure to much delayed onset of neuropathological changes in senescence have been reported [21]. These include miR-146a and miR-29b which inhibit the activity of the transcription factor SP1 promoting overexpression of inflammation-related genes [22]. However, the many gene targets of a single microRNA can complicate interpretation of changes in their levels [23].

Tin

Trimethyltin salts are able to penetrate the brain by virtue of the amphiphilicity. This organometal leads to activation of astroglia and microglia resulting in increased expression of genes involved in the inflammatory response together with decreased expression of genes of antioxidant enzymes [24]. The especial vulnerability of the hippocampus to trimethyltin salts suggests that neuronal activity plays a role in determining the extent of toxicity.

Metals and metalloids which form colloids and provide a surface for loose chelation of transition metals

The biologically relevant members of this class are silicon and aluminum. Both do not form true solutions, but rather colloidal suspensions which are chemically rather inert.

Aluminum and silicon

The promotion of oxidant and inflammatory events within the brain by Al is substantiated from both in vitro sources and whole animal studies [25]. Exposure of astrocytes to several types of Al-containing adjuvants invariably led to a large increase in production of inflammatory cytokines IL-6 and TNF-α [22,26,27]. Levels of Al salts in the drinking water of mice paralleling those found in some human water supplies can lead to increased indices of cortical inflammation.

An elevated amount of Al around amyloid plaques and cerebral vasculature has been found in cases of familial AD compared with control tissues from donors without neurological impairment or neurodegeneration [28]. Thus, support for Al being causal to promotion of cerebral inflammatory events and to increased incidence of AD emerges from a concordance of epidemiological and laboratory results [29].

Si-containing compounds do not readily access the brain, and evidence for the inflammatory nature of silica comes largely from inhalation of mineral particles into the lung. It is mentioned here as invoking a likely parallel mechanism for the furthering of neurotoxicity of redox-ambivalent metals by aluminum. Silica particles retained within the lung gradually complex increasing amounts of Fe, and this is associated with an elevated capacity to induce inflammatory processes [30]. The inflammatory properties of Al within the central nervous

system may well involve parallel mechanism, as colloidal aluminum in isolated systems greatly increases the free radical–producing ability of traces of Fe and Cu and can promote aggregation of amyloid-β peptide [29].

Complex metal-containing particulates

There is increasing evidence of the ability of airborne particulate material to access the brain and bring about inflammatory changes there [31]. Pollutant nanoparticles have many constituents including a range of metals. Their toxicity is attributable to both their physical structure with a large surface area and small enough size to allow intracellular penetration toxicity together with their chemical constitution [32]. The general direction of change in the brain afterexposure to urban polluted air is that nuclear content of the Nrf-2 transcription factor becomes depressed, leading to less activity of the antioxidant response element (ARE), thereby reducing expression of a battery of antioxidant and anti-inflammatory genes. Conversely, levels of the more proinflammatory transcription factors such as NF-κB are enhanced [31]. The overall result of these changes is a heightening of inflammatory and oxidant activity in the brain [31]. These laboratory findings parallel results of microarray analysis of frontal cortex of children and young adults from cities with differing levels of air pollution [33]. The soluble components superficially bound to airborne fine particulate matter include several transition metals, and such crude extracts can induce oxidant and inflammatory events in isolated cells [34]. Nanoparticle surfaces also contain volatile organic constituents which can also contribute to their toxicity [35]. Unsurprisingly, synergistic toxicological effects of components of particulate matter have been reported [36]. Similar to colloids, nanoparticles can bind transition metals with a low affinity, and the complexes formed from this partial chelation are capable of catalyzing highly active redox cycling [37]. Indeed, transition metals in the absence of binding ligands are very stable [38]. Recently, nanoparticles rich in iron and aluminum have been found within mitochondria in postmortem analysis of young children and young adults highly exposed to polluted air [39]. While these findings focus on cardiac and pulmonary tissues, it would be useful to examine corresponding brain preparations in a likewise manner.

Discussion and conclusions

While the exact sequence of events by which many metals provoke inflammatory responses within brain tissue is unknown, some general statements can be made.

1. All metals discussed possess the ability to enhance ROS although by various mechanisms. Thus, it is likely their ability to promote neuroinflammation is preceded by oxidant events. However, the close relation between neuroinflammation and production of excess oxidant free radicals (ROS) within the brain renders the definition of a causal sequence between these difficult to identify. That there is a bidirectional relationship between these entwined events is well-illustrated in the case of microglia. Oxidative stress initiates microglial inflammatory responses [40], and systemic inflammation leads to evidence of excess oxidant activity within microglia [41].
2. The presence of toxic metals or abnormal levels of essential trace metals may also directly alter the configuration of key proteins in the nervous system, such as amyloid-β peptide and amyloid precursor protein (APP). This can result in their altered folding and aggregation leading to activation of inflammasomes, such as the NLRP3 [42].
3. While inflammation caused by toxic metals is generally not confined to the brain, some of their most harmful effects are often expressed in nervous tissue. This is particularly true of low-level, long-term exposures. These are more common presently as most acute toxic exposures have largely been contained.
4. Interactions between small amounts of transition metals with colloids or particulates containing relatively inert metals can substantially magnify or enhance the generation of free radicals. This can then initiate glial inflammatory reactions. Such interfaces can make the toxicity of impure mixtures much greater than the sum of their constituents.
5. Future developments in understanding the mechanisms underlying metal-related neuroinflammation are likely to involve epigenetic modifiers of gene expression such as microRNAs specific for modifying immune responses. Focus on this area may also lead to emergence of novel therapeutic strategies [43,44].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest

1. Ding S, Li M, Gong H, Zhu Q, Shi G, Zhu A: **Sensitive and selective measurement of hydroxyl radicals at subcellular level with tungsten nanoelectrodes**. *Anal Chem* 2020, **92**: 2543–2549. https://doi.org/10.1021/acs.analchem.9b04139.

2. Town RM, van Leeuwen HP, Duval JFL: **Rigorous physicochemical framework for metal ion binding by aqueous nanoparticulate humic substances: implications for speciation modeling by the NICA-donnan and WHAM codes**. *Environ Sci Technol* 2019, **53**:8516–8532. https://doi.org/10.1021/acs.est.9b00624.

3. Saporito-Magriñá C, Musacco-Sebio R, Acosta JM, *et al.*: **Copper(II) and iron(III) ions inhibit respiration and increase**

free radical-mediated phospholipid peroxidation in rat liver mitochondria: effect of antioxidants. *J Inorg Biochem* 2017, **172**:94–99. https://doi.org/10.1016/j.jinorgbio.2017.04.012.

4. Ward RJ, Crichton RR: **Ironing out the brain**. *Met Ions Life Sci* 2019, **19**. https://doi.org/10.1515/9783110527872-010. books/9783110527872/9783110527872-010/9783110527872-010.xml.

5. Zhang XY, Cao JB, Zhang LM, Li YF, Mi WD: **Deferoxamine attenuates lipopolysaccharide-induced neuroinflammation and memory impairment in mice**. *J Neuroinflammation* 2015, **12**:20. https://doi.org/10.1186/s12974-015-0238-3.

6. Yauger YJ, Bermudez S, Moritz KE, Glaser E, Stoica B, Byrnes KR: **Iron accentuated reactive oxygen species release by NADPH oxidase in activated microglia contributes to oxidative stress in vitro**. *J Neuroinflammation* 2019, **16**:41. https://doi.org/10.1186/s12974-019-1430-7.

7. * Huat TJ, Camats-Perna J, Newcombe EA, Valmas N, Kitazawa M, Medeiros R: **Metal toxicity links to Alzheimer's disease and neuroinflammation**. *J Mol Biol* 2019, **431**: 1843–1868. https://doi.org/10.1016/j.jmb.2019.01.018.
This paper reviews the inflammatory potential of many neurotoxic metals and suggests mechanisms by which how they may contribute to the onset of neurodegenerative disease

8. * Hsu HW, Bondy SC, Kitazawa M: **Environmental and dietary exposure to copper and its cellular mechanisms linking to Alzheimer's disease**. *Toxicol Sci* 2018, **163**:338–345. https://doi.org/10.1093/toxsci/kfy025.
This paper illustrates how neurotoxic metals can enhance inflammation by changing the M2 quiescent glial phenotype to an M1 form. manufacturing a range of pro- inflammatory factors

9. Vasilyev VB: **Looking for a partner: ceruloplasmin in protein-protein interactions**. *Biometals* 2019, **32**:195–210. https://doi.org/10.1007/s10534-019-00189-1.

10. HaMai D, Bondy SC: **Oxidative basis of manganese neurotoxicity**. *Ann N Y Acad Sci* 2004, **1012**:129–141. https://doi.org/10.1196/annals.1306.010.

11. Chen J, Su P, Luo W, Chen J: **Role of LRRK2 in manganese-induced neuroinflammation and microglial autophagy**. *Biochem Biophys Res Commun* 2018, **498**:171–177. https://doi.org/10.1016/j.bbrc.2018.02.007. 2018.

12. Yin L, Dai Q, Jiang P, *et al.*: **Manganese exposure facilitates microglial JAK2-STAT3 signaling and consequent secretion of TNF-a and IL-1β to promote neuronal death**. *Neurotoxicology* 2018, **64**:195–203. https://doi.org/10.1016/j.neuro.2017.04.001.

13. Kirkley KS, Popichak KA, Afzali MF, Legare ME, Tjalkens RB: **Microglia amplify inflammatory activation of astrocytes in manganese neurotoxicity**. *J Neuroinflammation* 2017, **14**:99. https://doi.org/10.1186/s12974-017-0871-0.

14. Comes G, Manso Y, Escrig A, Fernandez-Gayol O, Sanchis P, Molinero A, Giralt M, Carrasco J, Hidalgo J: **Comes G, Manso Y, Escrig A, et al. Influence of Transgenic Metallothionein-1 on Gliosis, CA1 Neuronal Loss, and Brain Metal Levels of the Tg2576 Mouse Model of Alzheimer's Disease**. *Int J Mol Sci* 2017, **18**:251. https://doi.org/10.3390/ijms18020251. 2017.

15. * Muniroh M: **Methylmercury-induced pro-inflammatory cytokines activation and its preventive strategy using anti-inflammation N-acetyl-l-cysteine: a mini-review**. *Rev Environ Health* 2020, **35**:233–238. https://doi.org/10.1515/reveh-2020-0026.
This paper illustrates the bi-directional relation between inflammatory changes and rates of production of reactive oxygen species

16. Teixeira FB, de Oliveira ACA, Leão LKR, *et al.*: **Exposure to inorganic mercury causes oxidative stress, cell death, and functional deficits in the motor cortex**. *Front Mol Neurosci* 2018, **11**:125. https://doi.org/10.3389/fnmol.2018.00125.

17. Siblerud R, Mutter J, Moore E, Naumann J, Walach H: **A hypothesis and evidence that mercury may be an etiological factor in Alzheimer's disease**. *Int J Environ Res Publ Health* 2019, **16**:5152. https://doi.org/10.3390/ijerph16245152.

18. Vahter ME, Mottet NK, Friberg LT, Lind SB, Charleston JS, Burbacher TM: **Demethylation of methyl mercury in different brain sites of Macaca fascicularis monkeys during long-term subclinical methyl mercury exposure**. *Toxicol Appl Pharmacol* 1995, **134**:273–284. https://doi.org/10.1006/taap.1995.1193.

19. Cavanaugh R: **The dangers of dimethylmercury**. Feb *Chem World* 2019, **19**.

20. Shvachiy L, Geraldes V, Amaro-Leal Â, Rocha I: **Intermittent low-level lead exposure provokes anxiety, hypertension, autonomic dysfunction and neuroinflammation**. *Neurotoxicology* 2018, **69**:307–319. https://doi.org/10.1016/j.neuro.2018.08.001.

21. * Masoud AM, Bihaqi SW, Machan JT, Zawia NH, Renehan WE: **Early-life exposure to lead (Pb) alters the expression of microRNA that target proteins associated with Alzheimer's disease**. *J Alzheimers Dis* 2016, **51**:1257–1264. https://doi.org/10.3233/JAD-151018.
This paper reveals the importance of microRNAs in modulating responses to toxic metals. It also indicates the need to consider lifetime toxicity where deficits incurred during development may re-emerge with senescence

22. Lukiw WJ: **microRNA-146a signaling in Alzheimer's disease (AD) and prion disease (PrD)**. *Front Neurol* 2020, **11**:462. https://doi.org/10.3389/fneur.2020.00462.

23. Martin NA, Hyrlov KH, Elkjaer ML, *et al.*: **Absence of miRNA-146a differentially alters microglia function and proteome**. *Front Immunol* 2020, **11**:1110. https://doi.org/10.3389/fimmu.2020.01110.

24. Ferraz da Silva I, Freitas-Lima LC, Graceli JB, Rodrigues LCM: **Organotins in neuronal damage, brain function, and behavior: a short review**. *Front Endocrinol* 2018, **8**:366. https://doi.org/10.3389/fendo.2017.00366.

25. Zhang H, Wang P, Yu H, *et al.*: **Aluminum trichloride-induced hippocampal inflammatory lesions are associated with IL-1β-activated IL-1 signaling pathway in developing rats**. *Chemosphere* 2018, **203**:170–178. https://doi.org/10.1016/j.chemosphere.2018.03.162.

26. Shardlow E, Mold M, Exley C: **Unraveling the enigma: elucidating the relationship between the physicochemical properties of aluminium-based adjuvants and their immunological mechanisms of action**. *Allergy Asthma Clin Immunol* 2018, **14**: 80. https://doi.org/10.1186/s13223-018-0305-2.

27. Nies I, Hidalgo K, Bondy SC, Campbell A: **Distinctive cellular response to aluminum based adjuvants**. *Environ Toxicol Pharmacol* 2020, **78**:103404. https://doi.org/10.1016/j.etap.2020.103404.

28. Mold M, Linhart C, Gómez-Ramírez J, Villegas-Lanau A, Exley C: **Aluminum and amyloid-β in familial Alzheimer's disease**. *J Alzheimers Dis* 2020, **73**:1627–1635. https://doi.org/10.3233/JAD-191140.

29. Bondy SC, Campbell A: **Aluminum and neurodegenerative diseases**. *Adv Neurotoxicol* 2017, **1**:135–156.

30. Shimizu Y, Dobashi K, Nagase H, *et al.*: **Co-localization of iron binding on silica with p62/sequestosome1 (SQSTM1) in lung granulomas of mice with acute silicosis**. *J Clin Biochem Nutr* 2015, **56**:74–83. https://doi.org/10.3164/jcbn.14-44.

31. Haghani A, Cacciottolo M, Doty KR, *et al.*: **Mouse brain transcriptome responses to inhaled nanoparticulate matter differed by sex and APOE in Nrf2-Nfkb interactions**. *Elife* 2020, **9**, e54822. https://doi.org/10.7554/eLife.54822.

32. Schraufnagel DE: **The health effects of ultrafine particles**. *Exp Mol Med* 2020 Mar, **52**:311–317. https://doi.org/10.1038/s12276-020-0403-3. PMID: 32203102; PMCID: PMC7156741.

33. * Calderón-Garcidueñas L, Torres-Jardón R, Kulesza RJ, *et al.*: **Alzheimer disease starts in childhood in polluted Metropolitan Mexico City. A major health crisis in progress**. *Environ Res* 2020, **183**:109137. https://doi.org/10.1016/j.envres.2020.109137.
This review reports that inhalation iron-rich nanoparticles form polluted urban air, leads to cognitive impairment and early appearance of markers of Alzheimer's disease in young subjects

34. Xu F, Shi X, Qiu X, *et al.*: **Investigation of the chemical components of ambient fine particulate matter (PM2.5) associated**

with in vitro cellular responses to oxidative stress and inflammation. *Environ Int* 2020, **136**:105475. https://doi.org/10.1016/j.envint.2020.105475.

35. Keebaugh AJ, Sioutas C, Pakbin P, Schauer JJ, Mendez LB, Kleinman MT: **Is atherosclerotic disease associated with organic components of ambient fine particles?** *Sci Total Environ* 2015, **533**:69–75. https://doi.org/10.1016/j.scitotenv.2015.06.048.

36. Ljubimova JY, Braubach O, Patil R, *et al.*: **Coarse particulate matter (PM2.5-10) in Los Angeles Basin air induces expression of inflammation and cancer biomarkers in rat brains**. *Sci Rep* 2018, **8**:5708. https://doi.org/10.1038/s41598-018-23885-3.

37. Bondy SC: **Biometals**. In *Biometals in neurodegenerative diseases: mechanisms and therapeutics*. Edited by White AR, Aschner M, Costa LG, Bush AI, Oxford, U.K.: Elsevier; 2017:89–93.

38. Miller CJ, Rose AL, Waite TD: **Importance of iron complexation for fenton-mediated hydroxyl radical production at circumneutral pH**. *Frontiers in Marine Science* 2016, **3**. https://doi.org/10.3389/fmars.2016.00134.

39. Maher BA, González-Maciel A, Reynoso-Robles R, Torres-Jardón R, Calderón-Garcidueñas L: **Iron-rich air pollution nanoparticles: an unrecognised environmental risk factor for myocardial mitochondrial dysfunction and cardiac oxidative stress**. *Environ Res* 2020, **188**:109816. https://doi.org/10.1016/j.envres.2020.109816.

40. * Peng X, Li C, Yu W, *et al.*: **Propofol attenuates hypoxia-induced inflammation in BV2 microglia by inhibiting oxidative stress and NF-κB/Hif-1α signaling**. *BioMed Res Int* 2020, **2020**:8978704. https://doi.org/10.1155/2020/8978704.
This paper shows that reducing oxidative stress can lower the intensity of inflammation

41. Song S, Jiang L, Oyarzabal EA, *et al.*: **Loss of brain norepinephrine elicits neuroinflammation-mediated oxidative injury and selective caudo-rostral neurodegeneration**. *Mol Neurobiol* 2019, **56**:2653–2669. https://doi.org/10.1007/s12035-018-1235-1.

42. De Benedictis CA, Vilella A, Grabrucker AM: **The role of trace metals in Alzheimer's disease**. In *Alzheimer's disease [Internet]*. Edited by Wisniewski T, Brisbane (AU): Codon Publications; 2019 Dec 20 [Chapter 6]. PMID: 31895516.

43. Liu GJ, Zhang QR, Gao X, *et al.*: **MiR-146a ameliorates hemoglobin-induced microglial inflammatory response via TLR4/IRAK1/TRAF6 associated pathways**. *Front Neurosci* 2020, **14**:311. https://doi.org/10.3389/fnins.2020.00311.

44. Wang T, Zhang J, Xu Y: **Epigenetic basis of lead-induced neurological disorders**. *Int J Environ Res Publ Health* 2020, **17**:4878. https://doi.org/10.3390/ijerph17134878.