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Metals and Neuroinflammation

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Abstract

The presence within the brain of metal compounds at toxic levels, has adverse consequences for cerebral function. The type of damage that can be incurred often includes the presence of excessive amounts of inflammation. This event does not enhance cerebral defense systems and is thus not an effective or relevant response. On the contrary, such prolonged neuroinflammation can be disruptive to normal brain metabolism. This review outlines several means by which metals can bring about such extended and inappropriate immune activation within the CNS. Various mechanisms that may enable these changes will be discussed, including the formation of haptens, the production of reactive oxygen and nitrogen species, the sequestering of reducing capacity and the formation of inflammation-provoking colloids. Emphasis is given to the critical nature of the exact form of the metal exerting harmful effects. This can affect both access to, and subsequent disposition within the brain. The interaction of exposure to toxic metals with normal aging events is also considered.

Key words: Inflammation, Brain, Toxicity, Heavy Metals, Oxidative Stress, Aging

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Introduction

Inflammation represents the reaction of the body to factors that may be harmful and is a protective attempt to minimize damage by materials with potentially injurious qualities. The goal is the removal of harmful processes including aberrant cells, bacterial pathogens, and irritating materials. Inflammation is a constituent of both the innate and the adaptive immune systems and can be an important component of healing processes. Ideally, inflammation is an acute event lasting for only a few days, triggered by infection or physical injury. A less desirable event is chronic inflammation, which can be triggered in autoimmune disorders, non-degradable pathogens or by long-lasting pathological conditions. Such detrimental extended responses can lead to tissue destruction and infiltration of affected areas by fibrous cells.

In the brain, in addition to disease-related extended inflammation, there is evidence that aging is associated with an enduring elevation of inflammatory changes, even in the absence of known provocative factors¹. These heightened immune events appear even further exacerbated in several neurodegenerative disorders found with senescence. These include Alzheimer's and Parkinson's disease and also stroke^{2,3}. The cause of most age-related neurological disease is unclear. In the large, such disorders cannot be accounted for in genetic terms and they are thus likely to involve environmental influences. A range of laboratory-based studies, together with epidemiological findings, suggest that such deleterious environmental materials provoking excess immune activity within the brain, are likely to include several metals.

Mechanisms by which metal elements can incite immune activity

They are several means by which metal species may provoke disproportionate immune reactions. Although there is a distinctive sequence of events characterizing each mode of action, discussed below, several metals belong to more than one of these groupings.

2. Metals as haptens

Some xenobiotic metals can act as haptens by complexing with normal proteins. Such complexes can then stimulate the production of antibodies that may not only interact with the complex but also the original tissue protein can now act as an antigen. This can develop into a widespread autoimmune activation. While metals can act as haptens and provoke inflammatory activity, they largely involve tissues coming into direct contact with exogenous metals such as skin and lung⁴. There are few reports on this type of toxicity affecting the nervous system. However, developmental exposure to methyl mercury or mercuric chloride can lead to autoimmune responses to brain antigens⁵.

2. Metal elements with valence instability

Some metals can change valence under physiological conditions and these fluxes can catalyze the production of reactive oxygen species. Most of these metals, including iron, copper and manganese also have essential biological role, which can also depend on this property. Under normal physiological conditions, this attribute allows safe flow of electrons through the electron transport chain and a means of performing protected

oxidation and reduction reactions. However, in the unregulated presence of these free ions, the production of oxidant radicals (ROS, reactive oxygen species) can take place, by promoting redox activity. This can then activate immune activity and empower unchecked inflammatory processes.

Major metals in this grouping are Fe, Cu, Mn and Cr, all of which are also essential for normal cell metabolism. The intracellular distribution and binding of these metals is tightly controlled under normal circumstances and so only under pathological conditions are these constraints disrupted. Abnormal homeostasis of Fe and Cu appears associated with both Alzheimer's and Parkinson's diseases⁶. Both Cu and Fe levels are elevated in the Alzheimer's brain⁷.

Copper (Cu)

The harmful effects of excessive levels of copper are very apparent in Wilson's disease. This is a genetic disorder in which excessive copper, normally excreted or tightly bound to ceruloplasmin, accumulates in tissues⁸. In addition to a range of systemic effects, this disorder involves extensive brain damage⁹. The levels of markers of oxidative stress correspond with the clinical severity of the disease¹⁰. Environmental levels of copper may also be neurologically harmful. Low levels of copper in the drinking water of experimental animals can cause an inflammatory response in the brain¹¹ and also enhances levels of amyloidogenesis in a mouse model of Alzheimer's disease¹². The processes underlying this include activation of microglial NF- κ B and consequent release of TNF- α and nitric oxide and superoxide¹³.

Iron (Fe)

Similarly, in situations where intracellular iron concentrations are abnormally elevated, elevated levels of generation of damaging reactive oxygen species are found^{14,15}. The heightened neuroinflammation found in multiple sclerosis may be associated with excess iron deposition¹⁶.

The potency of iron in catalyzing redox-related ROS production is greatly enhanced by its partial sequestration on the surfaces of colloidal and particulate material, discussed in a later section.

Manganese

This metal differs from Fe and Cu in that both oxidant and reductive properties have been observed. Unlike the reduced forms of Cu and Fe, Mn²⁺ is resistant to oxidation and does not have strong reducing activity. The symmetry of its half-filled 3d shell may account for the reluctance of Mn²⁺ to lose one of its five d-electrons, and for its poor reducing ability¹⁷. However, in the presence of Mn³⁺ at 1/500 of the concentration of Mn²⁺, Fenton redox cycling with strong ROS producing capacity can take place^{18,19}. The ability of Mn³⁺ to dismutate into the divalent and tetravalent forms can lead to formation of Mn oxo-bridged complexes²⁰). These may form a colloidal suspension providing a large surface area thus further promoting oxidant reactions, described in a following section.

3. Metals attaching to sulfhydryl residues

Metals such as mercury and cadmium, which have a high affinity for sulfhydryl groups, can bind to important anti-oxidant molecules such as lipoate and glutathione, effectively blocking their free radical quenching ability. This can result in a reduced detoxification of, and thus excessive presence of short-lived reactive oxygen species. In addition to damaging macromolecules, such oxidant species can summon and activate immune-competent cell types, represented in the nervous system by microglia, astroglia and mast cells. Mast cells are found in sites of demyelination within the plaques of patients with multiple sclerosis and thus can also promote inflammation within the brain²¹. In addition, mast cells are found in the CNS. Like microglia, mast cells are derived from hematopoietic cells that migrate to the brain before closure of the blood brain barrier²². By this means oxidant events can enhance the development of inflammation. Important metals with strong affinity for –SH groups include Hg, Cd and Pb. The neurological consequences of exposure to these metals include initiation of glial immune reactions²³.

Lead (Pb)

Exposure of neonatal primates to lead can result in amyloid and tau deposition several decades later, in aged animals long after the cessation of any contact with Pb^{24,25}. These changes are associated with up-regulation of genes associated with the pro-inflammatory genes related to the immune response²⁶. Permanent functional sequelae following neonatal exposure to lead or methyl mercury have also been reported²⁷. Since Nrf-2, which facilitates expression of several anti-oxidant enzymes, appears to be protective²⁸, it is likely that any inflammatory effects such as induction of GFAP and release of

inflammatory cytokines, are preceded by oxidative events leading to activation of phospholipase A2^{29,30}. While these are generally considered harmful events, glial release of graded amounts of these cytokines in response to heavy metals may activate neurons in a protective manner^{31,32}. Both the extent and duration of the inflammatory response can determine whether it results in a beneficial or deleterious outcome. Neonatal exposure to lead has been reported to disrupted microglial development without leading to neuroinflammation³³, but a very similar study has found Pb to upregulate inflammatory genes³⁴. There appears to be a fine balance between the disruption of ontogenesis by Pb and its ability to enhance inflammatory processes in surviving cells.

Lead is undoubtedly a significant competitor with calcium and zinc and has an affinity for –SH groups. These may lie beneath its capacity for disruption of mitochondrial function, and inhibition of many key enzymes including synthesis of bipterin (essential for synthesis of catecholamine neurotransmitters). The complexity of lead toxicity and large range of targets impacted makes difficult the assigning of the relative importance of neuroinflammation in contributing to its overall harmfulness. However, lead has a much greater affinity for Zn than for Ca binding sites and this makes zinc finger proteins and δ -aminolevulinic acid dehydratase vulnerable to femtomolar concentrations of lead³⁵.

These levels are several orders of magnitude below those required to disturb calcium metabolism. The GATA zinc finger protein that restrains autoimmune events and confines inflammatory events, binds Pb tightly, leading to a decreased ability to bind to DNA and activate transcription³⁶.

Both lead and mercury induce glial cell reactivity; a hallmark of brain inflammation and

this may form the basis for promotion of Alzheimer's disease³⁷. While there is a barrier preventing many materials from crossing from the circulation to the CNS, there is nonetheless a continual interplay between glial elements and the peripheral immune system³.

Mercury (Hg)

Mercury has a high affinity for thiol (-SH) and seleno groups (-SeH) that are present in cysteine (a precursor for the biosynthesis of glutathione, the most prevalent intracellular antioxidant), lipoic acid, proteins, and enzymes. Selenium is critical for brain function and is present in 25 proteins that have selenocysteine at their active center. This element has both anti-oxidant and anti-inflammatory properties³⁸. Selenium administration may have clinical utility in the treatment of mercurial poisoning³⁹.

All forms of mercury, elemental, inorganic and organic are able to induce formation of reactive oxygen species and inflammatory responses within the brain. Thus inhaled Hg₀ depressed levels of antioxidant enzymes, superoxide dismutase and peroxidase and increased levels of oxidized glutathione in the mouse brain and this was accompanied by release of inflammatory IL-6⁴⁰. The anti-inflammatory, salicylic acid was protective and blocked these changes. Administration of either mercuric chloride or methylmercury to neonates can also evoke inflammatory changes in the brain but the underlying mechanisms may differ since only HgCl₂ induced the production of autoantibodies, which appear in the brain⁵. Pretreatment with dexamethasone can totally block some enzyme changes resulting from exposure to MeHg⁴¹. Methyl mercury has been shown to both

induce expression of genes for proteins related to inflammation (such as GFAP) and to inhibit expression of anti-oxidant genes (such as glutathione peroxidase)⁴². This simultaneous change in gene expression and the ability of both anti-oxidant and anti-inflammatory agents to be protective against mercurials, illustrates the close linkage between immune and oxidant events and the difficulty of establishing a sequential relation between them.

HgCl₂ is able to stimulate liberation of inflammatory cytokines from human mast cells, and this together with the use of ethylmercury as a preservative in some vaccines, has been suggested as a means by which low levels of Hg might contribute to the pathogenesis of autism spectrum disorder perhaps by way of activation of inflammatory mast cells⁴³. However the evidence for this is very limited.

Dimethyl mercury (Me₂Hg) is several orders of magnitude more lethal to humans and experimental animals than is monomethyl mercury (MeHgCl)⁴⁴. However, in isolated cell systems, the opposite is true, MeHgCl being much more toxic^{45,46}. This apparent contradiction illustrates the importance of two independent features of chemical neurotoxicity:

- a) The partition coefficients of toxicants will determine the rapidity of their accessing the brain. Generally, it is amphiphilic compounds such as ethanol and nicotine that exhibit maximal penetrance.
- b) The rate of biotransformation of absorbed materials is another key determinant of their toxicity. Such metabolism may enhance or diminish toxicity, or may initially

increase harmfulness and then act in a detoxifying manner.

Lipophilic Me_2Hg is absorbed across the skin or gut very rapidly and stored in fatty tissues, where gradually converted to the more toxic MeHgCl which ultimately accesses the brain. The penetrance of MeHgCl across tissue membranes is much lower but over time, it can gradually accumulate in tissues. This would account for the very long latencies encountered both after a single brief exposure to Me_2Hg or after extended low level exposure to MeHgCl ⁴⁷.

4. Metals associated with particulate and colloidal materials

A final class of metals appear rather inert, possessing no powerful affinity for sulfhydryl residues and no ability to change valence and little obvious reactivity. The key feature of this class is their presence in colloidal materials or nanoparticles, materials both endowed with a very large surface area. This can provide a site for the binding of traces of more redox-active metals whose incomplete sequestration greatly magnifies their redox-cycling abilities leading to major production of ROS⁴⁸.

Aluminum (Al)

A common metal of this class is aluminum, which exists within the cell either in colloidal form or as nanoparticles. Aluminum can promote amyloidogenesis by activation of NF- κ B and a specific miRNA⁴⁹. Very low levels of Al in drinking water, paralleling those found in reservoir supplies in some areas, have been found to promote neuroinflammation in experimental animals^{11,50}.

An important factor in enhancing the ROS producing potential of colloidal aluminum, is the presence of trace amounts of iron adhering to these particles. This is deduced from the finding that aluminum sulfate which has no ability in itself to promote ROS, can strongly stimulate the ROS-producing potential of very low concentrations of iron⁵¹. A similar interactive situation between a colloidal and a transition metal may pertain in the case of aluminum and copper⁵².

Titanium, Silver and Gold (Ti, Ag, Au)

Titanium dioxide nanoparticles can lead to oxidative stress in isolated microglial cell lines⁵³ and this can activate NF- κ B and lead to inflammation⁵⁴. Parallel findings have been reported using treated experimental animals⁵⁵.

A wide range of metallic oxide nanoparticles, including oxides of Ti, Fe, Zn, Cu and elemental Ag and Au, are able to cross the blood brain barrier and are suspected to be potentially neurotoxic. Both the surface chemistry and the shape of particles are relevant in establishing their degree of toxicity⁵⁶. The major mechanism of toxicity of these particles involves generation of oxidant free radicals which then activate transcription factors such as NF- κ B that precede inflammation⁵⁴. In the case of elemental Ag and Au, it is not established whether inflammatory changes caused by these elements are preceded by ROS production or not⁵⁷ especially as Au particles can also inhibit neuroinflammation in animal models of brain injury under some circumstances⁵⁸. The ability of Ag salts to bring about necrotic cell death may also be causal to the onset of inflammation⁵⁹.

The means by which these metals can promote ROS production and thence inflammation, is not readily apparent, but probably involves their colloidal nature under physiological

conditions. The presence of such finely distributed colloids can have two major consequences. Firstly, as they may be mistaken by the immune system for bacteria or material of bacterial origin, such dispersions are likely to promote phagocytic and oxidant activity. Since the particles cannot be cleared, such events can lead to a chronic inflammatory focus. A good parallel for this is found in the case of silicosis of the lung where an irresolvable mineral particle forms the basis for a source of persistent inflammation⁶⁰. Secondly, The large surface area of such colloidal particles, lends itself to the absorption of many materials on their outer surfaces. These materials may include redox active metals such as iron and copper. The pro-oxidant nature of such transition metals is greatly enhanced by their incomplete sequestration on surfaces of particulate materials. Again, silica can provide a useful example of the power of such interactions. Silica nanoparticles also only produce ROS in the presence of trace amounts of iron⁶¹. The toxicity of silica particles is strongly reduced by their prior washing in deferoxamine, a potent iron chelator. Thus traces of iron are likely to contribute powerfully to the ability of silica to promote inflammation. This attribute may be shared by other particles with a large surface area.

5. Metals which lead to oxidative stress and inflammation by means that are not yet understood

Some metals such as rare earths cerium (Ce) and lanthanum (Ln) can lead to the appearance of elevated levels of lipid peroxidation, inflammation and apoptosis in many tissues including the brain. While this involves major changes in gene expression including upregulation of a range of immune-related genes, the sequence of events by

which this takes place remains unknown⁶². However, it is possible that transcriptional pathways other than NFκB mediate between oxidative and inflammatory events⁶³.

The relation between reactive oxygen and nitrogen species and inflammation

There is a bidirectional connection between oxidant and inflammatory events. On the one hand inflammation often involves activation of microglial and astroglial elements within the brain, and this is associated with elevated levels of NADPH oxidase, which is a major source of superoxide anion production⁶⁴. Such superoxide, while relatively stable, if not rapidly detoxified by superoxide dismutase, can be converted to the very reactive hydroxyl radical.

On the other hand, there are several means by which a pro-oxidant milieu can be translated into activation of immune events. The transcription factor NFκB is at the crossroads between oxidative stress and derepression of pro-inflammatory genes. Several stimuli including reactive oxidizing species, effect the activation and translocation to the nucleus of NFκB, leading to enhanced glial expression of a broad range of genes relating to regulation of immune function. This includes genes for immunoreceptors, cytokines, chemokines, proteins involved in antigen presentation, acute phase genes, and stress response genes (such as iNOS). Increasing production of reactive oxidant species can up-regulate expression of diverse inflammatory mediators and the combination of these events can lead to brain injury⁶⁵. The glial inflammatory response that Cu²⁺ causes, includes release of nitric oxide, TNFα, activation of NF- B and its migration to the

nucleus. All these changes can be blocked by the antioxidant n-acetylcysteine¹⁴, indicating that at least in this case, oxidative stress precedes inflammatory changes. This report also implicates mitochondrial production of superoxide and thence hydrogen peroxide as the target of Cu. However, it must be borne in mind that the composition of NF- κ B dimers is critical in determining whether this transcription factor exerts predominantly beneficial and anti-apoptotic or inflammatory and pro-apoptotic effects. The NF- κ B/c-Rel dimer is predominantly protective while the NF- κ B/RelA dimer triggers expression of genes relating to apoptosis and neuroinflammation⁶⁶.

While oxidative stress and inflammation can interact in a synergistic manner, harmful events are generally limited by opposing homeostatic regulatory processes. One of these counterbalancing elements is the transcription factor Nrf2 which is redox-sensitive, activated under oxidant conditions and which reacts to these events by derepression of genes for antioxidant and detoxifying enzymes contained within the antioxidant response element (ARE)⁶⁷. Nrf2 is the predominant mediator of cellular responses to redox stress and is activated by cysteine thiols present as thiolate anions (S⁻), which are more reactive toward oxidant species than are sulfhydryl groups (-SH)⁴⁰. When homeostatic processes are overwhelmed, the prolonged appearance of highly reactive oxygen species caused by mechanisms based on the chemistry of various metals, described above can all lead to neuroinflammation.

Conclusion

The tight relation between oxidant and inflammatory events, also discussed in the section on mercury, makes difficult their clear separation. Metal-induced neuroinflammation and oxidative stress are inextricably intertwined, often rendering discussion of causal relationships speculative rather than definitive. It is however certain that metals can provoke undesirable inflammatory events that have a negative health outcome. The immune system is very sophisticated and its subtlety makes it prone to misinterpret events or to over-react to them. The evolution of the immune system has been largely determined by the development of a means to detoxify and remove adverse biological materials. These may be of exogenous origin (viruses and bacteria) or may have an endogenous source (abnormal cells). Many metal-based materials are not readily detoxified by immune mechanisms and their persistence can give rise to a detrimental chronic inflammatory state. The isolated nature of cerebral immune processes can make the brain especially vulnerable to such prolonged periods of immune hyperactivity.

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