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Neurochemistry of lead and manganese

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This themed issue highlights the cellular chemistry of two metal ions that are known to play deleterious roles in neurobiology: lead and manganese.

Themed issues at *Metallomics* serve several functions. They enable us to invite new communities that fit within the *Metallomics* scope: *Global approaches to metals in the biosciences encompassing environmental, analytical, bioinorganic and medicinal studies*, to contribute to the vibrant group of scholars who routinely read and publish in our journal. They allow us to highlight themes that emerge when the chemistry of metals is considered from a global perspective and to integrate the abundant scientific data into a coherent narrative, helping scholars, students, policy makers, and interested lay people.

We are delighted, then, to introduce the articles appearing in this themed issue.

Several papers in this themed issue draw attention to possible connections between early exposure to toxic metal ions and the development later of neurological diseases. Because metal ions can bind to regulatory elements, they have the potential to affect development in profound ways.

Jennifer Freeman and co-authors report that an embryonic lead exposure results in gender-specific changes in gene expression in the brains of aged zebrafish. The expression of genes in the brains of females was substantially more altered than in males. In females, the genes with altered expression were associated with nervous system development and function, including one set of genes associated with Alzheimer's disease; these were not seen to be altered in the male brain.¹

Jennifer Yang and co-authors present an overview of the neurotoxic effects of lead when it substitutes for calcium.² Lead toxicity is linked to its proclivity to substitute for one of two essential metal ions, calcium or lead. Yang *et al.*'s excellent overview of the literature details known interactions between lead and calcium binding proteins, allowing us to envision possible molecular bases for lead neurotoxicity.

Leal *et al.* present results from a study that shows a complex relationship between short-term neonatal exposure to manganese and the levels of tyrosine hydroxylase—and its degree of phosphorylation. Tyrosine hydroxylase catalyzes the hydroxylation of L-tyrosine to 3,4-

dihydroxyphenylalanine (L-DOPA). Tyrosine hydroxylase activity is regulated by phosphorylation of one or more serine residues.³ Tyrosine hydroxylase levels and the degree of phosphorylation were shown to vary as a function both of manganese dose and time lapsed since exposure.

Dean Wilcox, Rachel Narehood Austin, and co-authors present a detailed thermodynamic study of the binding of lead ions to the brain specific isoform of metallothionein, metallothionein-3 (MT-3),⁴ revealing that lead binds to MT-3 more tightly than zinc does, opening up the possibility that MT-3 plays a role in storing lead in the brain.

Jacqueline Ordemann and Rachel Narehood Austin present an overview of the connection between lead binding to zinc finger proteins and the development of mental illnesses later in life.⁵ The review is speculative because no studies connect all of the mechanistic steps between the *in vivo* binding of lead to a particular zinc finger protein to an increased chance of developing one of the brain-related diseases we profiled. However by pulling together various pieces of evidence from different types of study, the authors make clear that plausible chemical mechanisms exist that could link lead exposure to these metal illnesses with the hope that the suggested links will inspire research to further explore these potential connections.

Ashley Bush and co authors studied 1000 serum and erythrocyte samples, including 200 from victims of Alzheimer's Disease, and found that AD patients have significantly lower manganese levels in serum but no statistical difference in serum lead levels, suggesting that serum or erythrocyte metal levels are not good indicators of disease status.⁶

The article by Qi Ye and Jonghan Kim suggests a link between iron regulation and manganese toxicity. Their work hints at the possibility that a mutation already known to be linked to hereditary hemochromatosis might be protective against airborne exposure to manganese, which is an exposure route that leads to high Mn bioavailability.⁷

From the articles in this issue, we highlight several themes that emerge and questions that linger:

1. What biomolecules coordinate these metal ions as they traverse the various compartments inside living organisms? Do these biomolecules vary significantly among organisms?
2. How does the interplay between the thermodynamics of binding and the kinetics of binding and release play out?
3. How do the redox conditions of a cell affect metal availability? Are metal ions released under conditions of oxidative stress? Does the distribution of biomolecules that chelate metal ions change under these conditions?
4. How does nutritional status affect the availability of metal ions at the molecular level?

5. Do synergies—or antagonisms—exist between metal ions, *e.g.*, does the concentration of one metal ion affect the concentrations of proteins that can also bind other metal ions?

We also invite you to look at several articles that have appeared in prior issues of *Metallomics* that touch on these same themes.^{8–13}

There is good epidemiological evidence linking Pb and Mn exposure to a range of human health concerns, and good molecular data showing metal ion–biomolecule interactions. Just as always in studies of such complicated and interconnected systems, the challenge is to connect the microscopic with the global. *Metallomics* seeks to explore this middle region. We continue to publish work that goes beyond isolated studies of metal-containing biomolecules to deepen our understanding of the distribution, speciation, and reactivity of metals in biological systems. We particularly welcome papers describing advances in analytical techniques that facilitate the measurement of metal ion concentrations and speciation in complex biological matrices, and genomic/proteomic studies that provide a systemic view of the changes biological systems undergo with metal ion exposure.

We conclude by pointing out what is unfortunately obvious: these questions are simply not academic. Recently, policymakers in Flint, Michigan made the poorly informed decision to switch temporarily to a less expensive drinking water supply. This decision led to an increase in the number of children in Flint with elevated blood lead levels. It also led to a leap in awareness of the issue, and increased testing around the country that has, in turn, pointed to many other previously unknown lead hot spots. As city and regional managers make decisions about the benefits and costs of maintaining infrastructures and workplaces that do not expose occupants to toxic metals, a better understanding of the molecular connections between exposure and neurological health consequences will help inform their choices.

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