

It's All in the Metals

Report on the 3rd International Metals and Brain symposium at a combined meeting of the International Brain Research Organisation (IBRO), the Society of Neuroscientists of Africa (SONA), and the Collegium Internationale Neuro-psychopharmacologicum (CINP) in Cape Town, South Africa, 22 April 2005

Stefano L. Sensi^{a,b,*} and Susan van Rensburg^c

^aDepartment of Neurology, CESI-Center for Excellence on Aging, University 'G. d'Annunzio', Chieti, 66013, Italy

^bDepartment of Neurology, University of California, Irvine. Irvine, CA 92697-4292, USA

^cDepartment of Chemical Pathology, National Health Laboratory Service and Stellenbosch University, 7505 Tygerberg, South Africa

In the wonderful frame of Cape Town, neuroscientists from all over the world met to discuss the role of metals in brain function. The day was opened by a very intriguing plenary lecture from James Connor (Penn State University). The topic of this comprehensive talk was the role of iron dyshomeostasis in neurological diseases. Dr. Connor illustrated how iron unbalance could be linked to a variety of neurological conditions. Specifically, he discussed links of iron dyshomeostasis to Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and Hallorvorden-Spatz disease. All these conditions are associated with iron imbalance in terms of too much iron or limitations in iron storage capacity. Intriguing new data from cell culture models were presented showing how iron can enhance oxidative stress and inflammatory responses in microglia. He also described how a mutation in the HFE gene, commonly associated with hereditary hemochromatosis and iron overload disorders, is more prevalent in AD and ALS patients. Additionally, experimental evidence on the biological consequence of carrying the HFE mutation was presented. In the final part of the lecture, Dr. Connor also described how iron deficiency could, as well, lead to neurological diseases and discussed how iron deficiency during development can be associated with a myelin deficit that promotes a long lasting cognitive and motor impairment.

Also on the long lasting effects of iron deficiency, a very intriguing set of data presented by John Beard (Penn State University) indicated that dietary iron deficiency in early life is associated with persistent alterations in dopaminergic and serotonergic neurotransmission. According to Dr. Beard's data, these deficits continue to alter brain function despite later normalization of brain iron content and brain iron metabolism.

Quite an interesting story was presented by Susan van Rensburg (Stellenbosch University, South Africa) who discussed the role of iron in multiple sclerosis (MS). She opened with an extensive review on iron metabolism in MS, including the evidence for increased iron load in patients with MS. However, as pointed out by Dr. van Rensburg, in a subset of MS patients there is also experimental evidence for iron deficiency. Dr. van Rensburg presented data on the iron status of a group of MS patients, and also examined the effect of iron supplementation in iron deficient MS patients. The study from Dr. van Rensburg indicated significantly lower ferritin and transferrin concentrations in MS patients, and she also presented an MRI scan which shows improvement over 2 years of an MS patient taking iron supplements and other nutrients.

A more complex scenario emerged in the zinc session. Stefano Sensi (G. d'Annunzio University, Italy; University of California-Irvine), opened the session discussing the potent neurotoxic effects of intracellular free zinc. Intracellular accumulation of the cation can be the result of its translocation from pre-synaptic zincergic projections and/or cation mobilization from intracellular sites. Dr. Sensi reviewed pathways of injury

*Corresponding author. Tel.: +1 39 0871 541544; Fax: +1 39 0871 541542; E-mail: ssensi@uci.edu.

set in motion by intracellular free zinc and focused his attention on the potent effect of the cation in disrupting mitochondrial function.

Besides its potent neurotoxic effects, zinc may also be a key regulator of cell and circuitry functioning. In that respect, Gabriel Nowak (Institute of Pharmacology, Polish Academy of Sciences, Poland) presented a clinical study that supports the notion that zinc supplementation could be implemented as an antidepressant. Indeed, data from Dr. Nowak's group indicate that the cation may act as an enhancer of the positive effects promoted by classical selective serotonin reuptake inhibitors.

The zinc session was closed by a talk by Felix Potocnik, (Stellenbosch University, South Africa) who analyzed the role of zinc supplementation in AD. Quite interestingly, preliminary data from Dr. Potocnik seem to indicate that zinc supplementation can produce cognitive improvement in AD patients.

These presentations are a reflection of the current complexity surrounding the role of zinc in brain functioning and diseases, and strongly indicate that more data are needed to unravel the complex actions of this cation.

On the aluminum front, the energetic talk by Paolo Zatta (CNR, Italy) indicated how aluminum could greatly enhance human prion protein (PrP) oligomerization. Dr. Zatta started his presentation by reviewing conformational and aggregational changes of PrP induced by aluminum, copper, manganese, and zinc. Integrating previous findings from David Brown who found that manganese is an important trigger for PrP aggregation, data from Zatta's group indicate that aluminum and zinc are able to promote PrP aggregation with high efficiency. According to Dr. Zatta's data, the

two cations trigger aggregates in the form of intermediate circular oligomeric structures that evolve to fibrillar species. Denise Drago, also from Zatta's group, presented a very exciting set of data that show how zinc and aluminum could also cooperate in amyloid- β fibril formation.

Still on aluminum, another interesting talk by Mario Suwalsky (University of Concepcion, Chile) showed how the cation has a potent synergistic effect with amyloid- β in triggering structural perturbations of cell membranes. Dr. Suwalsky also discussed how these morphological changes can be a key step in the injurious cascade set in motion by the amyloid- β peptide.

Finally, Andrzej Szutowicz (University of Gdansk, Poland) talked about aluminum-triggered calcium deregulation, inhibition of pyruvate decarboxylation, decrease of acetyl-CoA content as well as acetylcholine content and release, in S56 cholinergic cells.

These findings could provide a link between aluminum toxicity and the preferential loss of cholinergic neurons observed in AD.

The end of the day was marked by a very enriching collegial discussion in which we reviewed the data presented throughout the symposium and put together a strategic plan for future research directions. One common motif emerged: the study of how metals can influence brain functioning needs a more integrated approach. A key issue, as pointed out by Dr. Zatta, is that dyshomeostasis of one specific metal produces immediate reverberating effects on the homeostasis of the others. All the speakers agreed that more effort should be spent in trying to integrate our findings.

Future Metals and Brain meetings will definitely represent the ideal setting for such an endeavor.