

## Editorial

# Metals and Alzheimer's Disease

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Research into the role of metals in Alzheimer's disease (AD) has rapidly advanced over the past two decades. Early studies described controversial links between trace metals and dementia. More recently, this concept has developed further with the understanding that a range of biometals and environmental metal toxins are likely to have a central role in determining the onset, progression, and clinical outcomes of AD and other forms of neurodegeneration. Key studies were instigated in the early 1990s by Ashley Bush and colleagues, demonstrating that metals such as zinc and copper were critical in amyloid beta ( $A\beta$ ) aggregation and (neuro)toxicity. Subsequent studies on metals in AD have opened up vast areas of research including the role for metals in amyloid precursor protein ( $A\beta$ PP) metabolism and processing,  $A\beta$  cleavage and degradation, synaptic  $A\beta$ -metal interactions, and neuroprotection associated with modulation of metal homeostasis.

In this issue we have provided a broad insight into some of these exciting areas of research, and the conclusion seems to be that a far greater level of understanding is still needed to allow development of treatments to halt the progression of AD. Tabner et al. and Kawahara and Kato-Negishi have described how interaction of  $A\beta$  with metals such as copper and iron is associated with (neuro)toxic action of small, soluble  $A\beta$  oligomers, likely mediated through generation of reactive oxygen species (ROS) and in particular, the highly reactive hydroxyl radical. In a related article, Yang et al. have provided valuable research into the importance of helical sheet formation in ROS generation associated with copper interactions. While metal interactions with  $A\beta$  are clearly

critical for its (neuro)toxic processes, metals also have a key role in generation of  $A\beta$ . Ho et al. have described research demonstrating that calcium and magnesium are required for  $\gamma$ -secretase activity, which is the final cleavage step in  $A\beta$  generation. An important, but still undefined role for iron in AD is supported by the study described by Squitti et al. where they associated ceruloplasmin/transferrin ratios and transferrin saturation with cognitive decline and increased oxidative stress in AD. A broad review by Salvador et al. brings together an interesting overview of how neurons handle iron and how iron dysregulation may lead to neuronal degeneration in AD. Likewise, zinc has a clear and important role in AD. It is involved in many processes central to the disease, including  $A\beta$ PP and  $A\beta$  processing and degradation, and zinc is released into the synapse where it can modulate neurotoxic action of  $A\beta$  and glutamate neurotoxicity, two factors that are closely associated with AD (Watt et al. and Takeda).

B. Weiss takes us in a different direction, reviewing the importance of exposure to environmental metals during development and their possible association with AD later in life. Such interactions may have key modulating roles in neurodegeneration and have not been adequately investigated. Of course, the aim of understanding metals in AD, like any AD research, is primarily to form the basis of potential therapeutic treatments. In relation to this, El Ghazi et al. describe interesting interactions between metallothionein and proteins associated with transport, signaling and chaperoning, highlighting the complexity of metal interactions

with AD, both direct ( $A\beta$ -metal) and indirect, through metallothionein. Amadoruge and Barnham review the potential modulation of membrane receptor function by metals. In addition, Srinivasan et al. report on the potential use of melatonin to provide neuroprotective action early in the course of AD. Finally, the paper by Braymer et al. highlights the importance of developing novel tools to investigate the role of metals in AD and has described the generation of molecules that may target  $A\beta$  and metals simultaneously. It is hoped that the research and reviews described here will help to update the AD research community on the state of play in regards to metals in AD and offer insights into where future research should be directed.

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