

Editor's Foreword

Metal ions are essential building blocks for life. However, they are also deeply implicated in pathological events related to their depletion or abnormal accumulation in human and animal tissues, mainly the brain, with consequent neurodegenerative phenomena. In the last three decades abundant scientific literature has attributed an important role to metal ions in neurodegenerative disorders such as Alzheimer's (AD), Parkinson's, Huntington's, Menkes' and Wilson's diseases, as well as amyotrophic lateral sclerosis, prion diseases and others. The first significant impact on the role of metal ions in neuropathology was when Professor Donald McLachlan, from the University of Toronto, Canada, proposed aluminum as a potential etiopathogenic factor in AD. So far thousands of papers have demonstrated the neurotoxic role of aluminum, but the direct connection between this metal ion and AD is still far from to be clearly demonstrated. However, in spite of some superficial and poorly documented conclusions, the debate is still open but the complexity of this issue, both in terms of the analytical determination of aluminum in human tissues, mainly in the brain, and the complexity of the aluminum chemistry makes this topic a *Vexata Questio* and rather a hard dilemma that will certainly not be solved in a short period of time [6]. On the other hand, the identification of the etiopathogenic agent/s for the vast majority of neurodegenerative diseases is also far from clear. In AD, for instance, the well known *amyloid cascade hypothesis*, so popular for several years as the major etiopathogenic mechanism, is nowadays at the centre of a wide-spread controversial debate. In this connection, it is noteworthy, that for AD, as well as other neurodegenerative diseases, except those demonstrated to be genetic in character (e.g., Menkes' and Wilson's), etiological factors are still a matter of intense investigation and several therapeutic strategies which aroused great interest in the recent past have been seriously questioned [1]. In addition, the AD vaccination approach, which is considered a promising final response, is by no means just around the corner, as was experienced for several other potential treatments from the NGF, the anticholinesterasic strategies and others some years ago. More than ever

before, what is required today is interdisciplinary and open minded studies.

Recently, copper has been strongly implicated in the etiopathogenesis of AD in association with amyloid- β [4], as well as in prion diseases [3]. However, the clinical results so far obtained on this hypothetical connection, in spite of an abundant and enthusiastic literature, remain rather controversial and elusive both in terms of etiopathogenesis and preliminary therapeutic treatments, with the so called *chelation therapy*, the chemistry of the various proposed chelators being little understood. Whether oxidative stress in concomitance with metal ion dismetabolism is the primary or secondary effect in the etiopathogenesis of AD as well as other pathogenic events is still to be established, since free radical production is a natural reaction in any pathological event [5], and an antioxidant defence strategy might be generally speaking beneficial anyway [2].

Metal ions have a strong impact as aggravating factors in neurodegenerative diseases in terms of oxidative stress and free radical production, protein misfolding phenomena, hyperphosphorylation mechanisms, metabolic alterations, etc., emphasising the potential role of the metal ions as important elements that could accelerate and /or aggravate the neuropathogenic events.

With this special issue, we wish to provide further evidence on the importance of the study of metal ions in neurological disorders, hoping that fresh blood will be pumped abundantly into this rather difficult and sometimes misunderstood topic. This hope derives pragmatically from the fact that several laboratories which were initially sceptical of the role of metal ions in pathogenic events related to neurodegenerative phenomena are now deeply involved in this field.

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References

- [1] S.O. Bachurin, Medicinal chemistry approaches for the treatment and prevention of Alzheimer's disease, *Medicinal Chem. Rev* 1 (2003), 48–88.

- [2] A. Campbell, M.A. Smith, L.M. Sayre, S.C. Bondy and G. Perry, Mechanisms by which metals promote events connected to neurodegenerative disease, *Brain Res Bull* **55** (2001), 125–132.
- [3] J. Sasson and D.R. Brown, Copper and prion disease, in: *Metal ions and neurodegenerative disorders*, P. Zatta, ed., World Scientific, Singapore, 2003, pp. 279–306.
- [4] A.L. Friedlich, H. Xudong, S. Nagano, J.T. Rogers, L.E. Goldstein, A.I. Bush, G. Multhaup, K. Beyreuther, W. Stremmel and T. Bayer, Importance of copper and zinc in Alzheimer's disease and the biology of amyloid- β protein and amyloid- β protein precursor, in: *Metal ions and neurodegenerative disorders*, P. Zatta, ed., World Scientific, Singapore, 2003, pp. 245–262.
- [5] B. Halliwell and J.M.C. Gutteridge, *Free radicals in biology and medicine*, 3 ed., Oxford Univ. Press, London, 2003.
- [6] T. Kiss, K. Gajda-Schranz and P. Zatta, The Role of Aluminium in Neurotoxic and Neurodegenerative Processes, in: *Metal Ions in Life Sciences*, (Vol. 1), A. Sigel, H. Sigel and R.K.O. Sigel, eds, Wiley & Sons, Chichester, 2006, (in press).