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A survey of different approaches using ESI Mass Spectrometry for the characterization of metal binding sites in amyloid peptide fragments.

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Neurodegenerative disorders (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD) and prion diseases are some of the most common forms of age-related diseases. Even if pathogenesis of these neurodegenerative diseases remains unclear, increasing evidences point out a common critical molecular process involving the assembly of various aggregated protein with a β-sheet conformation, termed amyloids.[1] The inhibition of this process could be a viable therapeutic strategy for the treatment of neurodegenerative diseases. Metal ions, especially copper, zinc and iron play a very important roles in neurodegeneration having impact on both protein structure and oxidative stress.[2] For a better comprehension of the structural features of the metal-amyloid protein complexes, our previous studies aimed at determining the stoichiometry, the affinity and the location of metal binding sites as well as the coordination environment around the metal ions.[3-6] In particular, potentiometric investigations were used to determine the stoichiometry and quantify the metal binding affinity of protein and/or peptide complex species. Moreover, the speciations resulting from thermodynamic data were coupled with spectroscopic information (UV–Vis, CD, ESR, NMR, and MS) in order to clarify the binding modes of various species. One of the main hindrances in amyloid protein investigation concerns the low peptide solubility at the concentrations needed to perform potentiometric titrations and spectroscopic studies. In this contest, the high sensitivity of mass spectrometry may overcome this limit. In this presentation, i will discuss the different mass spectrometry approach used in the characterization of metal ion complexes with different amyloid peptides such as prion,[4] Aβ,[5] Tau[6] and IAPP fragments. In particular, high-resolution ESI-MS assignments can be used to obtain direct information on stoichiometry of different metal complex species existing in dilute solutions. Tandem mass spectrometry investigations provides additional information regarding the metal interaction with amyloid peptide fragments. In particular, HCD (High energy Collision Dissociation) of copper(II) complexes, selected as precursor ions, provides interesting information about the amino acid residues involved in the copper(II) coordination. In order to evaluate the involvement of specific aminoacid residues in the formation of metal complexes, i will show some examples of limited proteolysis experiments together with ESI mass spectrometric analysis of peptide complexes.[4, 5]

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