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# MULTI-HISTIDINIC FRAGMENTS BINDING BIOLOGICAL METALS: AN NMR STUDY

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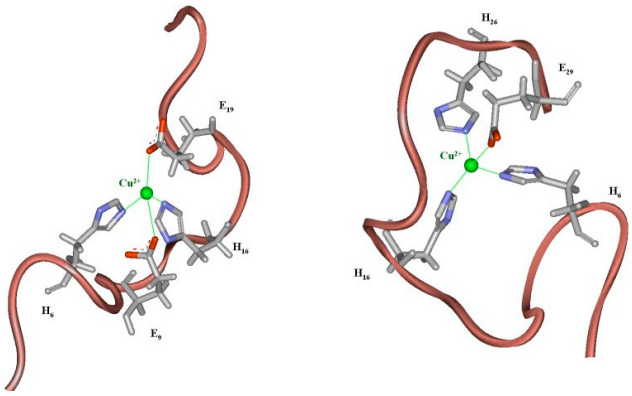
Cap43 protein can be considered as a "stress protein" since it is involved in a number of noxious events inside the cell, like hypoxia, cancerous states and metastasis suppression, and stress response just to quote some. Another interesting feature is that its expression is triggered by the rise in concentration of some metals, amongst which nickel gives the highest response [1].
We have examined the whole sequence of this protein in the search of a suitable site for metal binding, finding a remarkable aspect that prompted us to deepen our investigation. In fact, Cap43 presents in its C-terminal region a mono-histidinic decapeptide whose sequence is repeated consecutively three times (TRSRSHTSEG-TRSRSHTSEG-TRSRSHTSEG). The occurrence of such a repeated motif containing a histidine residue reminded us of neurodegenerative deseases and prions, where an octapeptide fragment bearing an histidine residue is repeated four times, and proved to be very active in binding Cu(II) ions, so that the tetra-repeat sequence is able to bind up to four metal ions. Another peptide, the β-amyloid fibril, contains a multi-histidinic sequence which seems involved in metal coordination within the process of aggregation. It is thus possible that also Cap43 could have a similar behaviour toward metals. We have used the 10-amino acid monohistidinic basic fragment (TRSRSHTSEG) and its two- and three-repeats to investigate their coordination mode towards metal ions such as Cu(II), Ni(II) and Zn(II). Multidimensional and multinuclear NMR techniques have been employed to uncover the details of metal coordination at different pH values and metal-to-ligand molar ratios. The data collected in our experiments allowed us to calculate structural models for the metal complexes, both at low and high pH-values[2-5].




A proposed $\{2N_{im},2O^-_{carbox}\},\{3N_{im}, O^-_{carbox}\}$ multi-histidinic copper models at "low" pH

[1] D.Zhou, K. Salnikow, M. Costa, *Cancer Res.* **58**, 2182-2189 (1988)
[2] M.A. Zoroddu, S. Medici, M. Peana, R. Anedda *Dalton Trans.* (2009) in press
[3] M.A. Zoroddu, S. Medici, M. Peana, *J Inorg Biochem.* (2009) in press
[4] M.A. Zoroddu, M. Peana, T. Kowalik - Jankowska, H. Kozlowski, *Dalton Trans.* **44,** 6127-6134 (2008)
[5] M.A. Zoroddu, M. Peana, T. Kowalik-Jankowska, H. Kozlowski, M. Costa, *J.Inorg.Biochem*. **98**, 931-939 (2004)