Zinc isotope investigations into neuropeptide aggregation

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The zinc isotope composition in brain tissue from healthy mice tends to become lighter with aging, whereas the effect is significantly less obvious with transgenic mice affected by the Alzheimer disease [1]. There is thus a Zn isotopic signature potentially marking this disease in mice brain. Although interesting, this global approach makes it difficult to understand the exact molecular mechanism responsible for such Zn isotope dynamics.

We therefore investigated this isotopic effect at the molecular scale to understand the biochemical reactions at play. Amyloid Beta (Aβ) peptide aggregation is a key process leading to plaques typical of brains affected by Alzheimer's disease. Transition metal ions such as Zn, Cu and Fe are known to be involved in this aggregation process, but the origin of these metals and the exact chemical reactions involved remain obscure [2].

We have conducted aggregation experiments of $A\beta_{40}$ and its simplified form $A\beta_{28}$ in the presence of Zn. Incubations were performed for 20h under agitation at pH 7.4, 37°C in the presence of Thioflavin-T to monitor the aggregation progress by fluorescence. Experiments were ran using different Aβ/Zn ratios and some involved dissolved aminoacids having different functional groups to monitor the effect of Zn exchange between aggregated Aβ and the ambient solution on δ^{66}Zn. Zinc concentration analysis by ICP-MS performed after sample centrifugation and mineralization revealed different distributions of Zn between the aggregated peptides and the supernatant depending on the nature of the peptide, Aβ/Zn ratio and amino acid added. Subsequent Zn purification and isotopic analyses by MC-ICP-MS revealed Δ^{66}Zn fractionation between peptide and supernatant ranging from nil to ~0.4‰. These preliminary results therefore illustrate that Aβ aggregation can influence δ^{66}Zn in brains.

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[2] E. Atrian-Blasco, P. Gonzales, A. Santoro, B. Alies, P. Faller & C. Hureau (2018) Coord. Chem. Rev., 371: 38-55.