Impact of Zinc in Alzheimer's disease at the molecular level

Coordination Chemistry Lab – UPR 8241 - Toulouse

Alzheimer's disease (AD) is one of the most serious diseases mankind is now facing as its social and economical impacts are increasing fastly. AD is very complex and the amyloid-β (Aβ) peptide as well as metallic ions (mainly copper and zinc) have been linked to its aetiology. While the deleterious impact of Cu is widely acknowledged, intervention of Zn is certain but still needs to be figured out.

The main objective of the present proposal, which is strongly anchored in the bio-inorganic chemistry field at interface with spectroscopy and biochemistry, is to design, synthesize and study new drug candidates (ligands L) capable of (i) targeting Cu(II) bound to Aβ within the synaptic cleft, where Zn is co-localized and (ii) disrupting the aberrant Cu(II)-Aβ interactions involved in ROS production and Aβ aggregation, two deleterious events in AD. The drug candidates should have high Cu(II) over Zn selectively to preserve the crucial physiological role of Zn in the neurotransmission process.

To reach this objective, it is absolutely necessary to first understand the metal ions trafficking issues in presence of Aβ alone at a molecular level (i.e. without the drug candidates).This includes: (i) determination of Zn binding sites to Aβ, impact on Aβ aggregation and cell toxicity, (ii) determination of the mutual influence of Zn and Cu to their coordination to Aβ, impact on Aβ aggregation, ROS production and cell toxicity.

Methods used will span from organic synthesis to studies of neuronal model cells, with a major contribution of a wide panel of spectroscopic techniques including NMR, EPR, mass spectrometry, fluorescence, UV-Vis, circular-dichroism, X-ray absorption spectroscopy...

Within in the framework of the ERC-StG 638712 - aLzINK proposal described above, the post-doctoral project aims at probing the impact of Zn, Cu and both in the aggregation of the Aβ peptide. The kinetics of the aggregation as well as the aggregates morphology will be studied. Toxicity of the various aggregates will be evaluated by classical MTT test on neuronal cells.

In a second and complementary part, the design, synthesis and studies of the ability of peptide-based or Schiff-base derivative ligands to remove Cu and restore cell viability are planned.

The candidate should be highly interested by multidisciplinary researches (chemistry – biology – biophysic), self-motivated and have strong skills in inorganic chemistry and physico-chemical studies.

Starting date: Oct. 2017 and no later than Dec. 2017.
Duration: up to 2 years.

Gross salary: 2500 Euros.

To apply, please send your CV and the names of three referees to christelle.hureau@lcc-toulouse.fr.