Chelation therapy in Alzheimer's disease: a switch from the Cu(II) target to the Cu(I) target

Charlene.esmieu@lcc-toulouse.fr

In the brains of patients with Alzheimer's disease, a neurodegenerative disease, copper ions are misregulated. Elevated concentrations of copper have been detected within senile plaques—one of the primary hallmarks of the disease—composed predominantly of the amyloid-beta (Aβ) peptide. The release and aggregation of Aβ are recognized as early and pivotal events in the progression of Alzheimer's.(1)

Studies have demonstrated *in vitro* that copper bound to Aβ (Cu–Aβ) can generate reactive oxygen species (ROS) in the presence of molecular oxygen and a reductant.(2) This oxidative activity of Cu–Aβ would exacerbate oxidative stress, a well-established driver of neuronal damage and disease progression. Moreover, it is now emerging that Cu interaction with Aβ would stabilize the oligomeric forms of Aβ which are considered as the most toxic forms nowadays.(3) As such, the dysregulation of copper and its interaction with Aβ is increasingly seen as a critical factor in the molecular pathology of Alzheimer's disease. In order to counterbalance the harmful effects of Cu bound to Aβ, researchers have developed a therapeutic approach known as chelation therapy.(4, 5) This involves the use of a ligand that is capable of extracting Cu(II) from the amyloid beta, thereby rendering it incapable of producing reactive oxygen species. A lot of Cu(II) chelators have been described in the scientific literature.(4) Despite the encouraging outcomes observed in vitro, in cells, and in model animals, the transition of the molecules to human trials has not been successful. One possible explanation for this is the lack of selectivity of the molecules for Cu(II) over Zn(II), an cation that is highly present in the synaptic cleft, where Aβ peptides are located.(4) In this context, we examine the potential of Cu(I) chelators, in parallel to Cu(II) chelators, to address this challenge. We present here the design, the synthesis and *in vitro* studies of ligands that target the Cu(I) in the context of Alzheimer's disease.(6)

Funding: ANR-20-CE07-0009

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