Molecular tweezer protects against alpha synuclein-induced neuronal toxicity

Emilie Faggiani*[1], Francesca De Giorgi[2], François Ichas[2], Benjamin Dehay[3], and Erwan Bezard[1]

[1]Institut des Maladies Neurodégénératives [Bordeaux] – Université de Bordeaux, Centre National de la Recherche Scientifique : UMR5293 – France

[2]INSERM U1084, Experimental and Clinical Neurosciences Laboratory, Cellular Therapies in Brain Diseases group – Université de Poitiers – France

[3]Institut des Maladies Neurodégénératives – CNRS : UMR5293, IMN-CNRS – France

Résumé

Introduction - Parkinson disease (PD) is characterized by the accumulation of aggregated forms of α - synuclein (α -syn) in intraneuronal cytoplasmic inclusions, named Lewy bodies (LB). The development of therapeutic strategies to prevent cell death in PD has been limited by a lack of understanding of the mechanisms driving neurodegeneration. However, increasing evidence based on the multiple roles ofα - syn in PD pathogenesis has suggested to consider several therapeutic strategies aiming at reducing α- synuclein toxicity. The prototypical molecular tweezer CLR01 has shown to inhibit aggregation and hence toxicity of multiple amyloidogenic proteins, suggesting as a potential target in PD therapy. Our objective was to study whether CLR01 could protect neurons from α -syn-induced pathology.
Materials and Methods - To test the ability of CLR01 to interfere with neuronal loss and pathology propagation, we used the human PD-derived α -syn seeding mouse model that recapitulates nigrostriatal loss and α-syn pathology propagation, 4 months post-inoculation. CLR01 was administered subcutaneously only during the last month. In parallel, to further understand the molecular mechanism of CLR01, we conducted a simple in vitro approach using pre-formed α-synuclein fibrils (PFFs) associated with a suitable seeding aggregation assay in cortical primary neurons.

Results - Our *in vivo* study confirmed a protective effect of CLR01 against dopaminergic neuronal cell death in this mouse model, associated with a reduction of α-syn aggregates burden. However, our *in vitro* results are suggestive for a more complex molecular mechanism: indeed, the molecular tweezer increased PFFs-induced α -syn phosphorylation at S129 in primary neuronal cultures, a characteristic landmark associated with pathology of α-syn.
Conclusions - Although molecular mechanism of CLR01 needs to be studied in-depth, the data we have collected so far suggest that the use of molecular tweezers CLR01 might be a promising approach for the treatment of synucleinopathies.

Mots-Clés: molecular tweezer, CLR01, alpha, synuclein, Parkinson

*Intervenant