NEW MULTIPOTENT DUAL INHIBITORS OF MAO AND ACHE/BUCHE AS PROMISING MOLECULES FOR THE TREATMENT OF ALZHEIMER’S DISEASE

I. Bolea¹, A. Gella², A. Samadi³, M. Unzeta¹, J.L. Marco-Contelles³

¹Bioquimica i Biologia Molecular, Universitat Autonoma de Barcelona, Barcelona, ²Faculty of Medicine and Health Sciences, International University of Catalonia, Sant Cugat del Vallès, ³Laboratorio de Radicales Libres y Quimica Computacional, IQOG, CSIC, Madrid, Spain

Introduction: The cholinergic theory of Alzheimer's disease (AD) suggests that the selective loss of cholinergic neurons results in a deficit of acetylcholine in specific brain regions that mediate learning and memory functions. However, alterations in other neurotransmitter systems, specially serotoninergic and dopaminergic, are also thought to be responsible for the behavioural disturbances observed in AD patients.

Aim: A new family of multi-target molecules able to interact with cholinesterases (ChE) as well as monoamino oxidases (MAO) has been synthesized and pharmacologically assessed.

Methods: We evaluated the capacity of compounds to inhibit MAO-A and B as well as AChE and BuChE. Moreover, we studied the capacity of inhibition of Ab (1-40 and 1-42) aggregation of the most promising compound by ThT method and TEM. Finally, we evaluated its antioxidant effect in the dopaminergic PC12 cells.

Results: The evaluation of the compounds showed that the most promising hybrid is a potent, irreversible, and non-competitive inhibitor of both MAO-A (IC₅₀ = 5.2 ± 1.1 nM) and MAO-B (IC₅₀ = 43.1 ± 7.9 nM), and a moderately potent mixed-type inhibitor of AChE (IC₅₀ = 0.35 ± 0.01 mM) and BuChE (IC₅₀ = 0.46 ± 0.06 mM). This molecule also prevents the Ab₄₂ self-aggregation (50.3 ± 3.7%) and the AChE-dependent aggregation of Ab₄₂ and Ab₄₀ (42.8 ± 4.5% and 21.3 ± 5.0%, respectively). Moreover this molecule has shown an antioxidant capacity.

Conclusions: These results suggest that one of these new hybrid compounds is a promising multi-target drug candidate with potential to modify the natural course of the disease.