THE ACETYLCHOLINESTERASE DONEPEZIL DIFFERENTLY AFFECTS THE EXPRESSION OF THE α7 NICOTINIC RECEPTOR, CHRNA7, AND ITS HUMAN-RESTRICTED DUPLICATED FORM, CHRFAM7A: IMPLICATIONS IN THE "CHOLINERGIC ANTI-INFLAMMATORY PATHWAY" ACTIVATION IN ALZHEIMER'S DISEASE

1)Benfante R. 2)Di Iascio S. 3)Maroli A. 4)Cardani S. 5)Locati M. 6)Drufuca L. 7)Fornasari D.

CNR - Neuroscience Institute

In the last years, increasing evidence has linked several neurodegenerative and psychiatric disorders to inflammation. Controlling neuro-inflammation has indeed become a promising approach to treat neuro-degenerative diseases. The Central Nervous System exerts a control on innate immunity through the “Cholinergic Anti-Inflammatory Pathway”, in which the splenic terminals of the Vagus nerve induce an anti-inflammatory response by stimulating the release of acetylcholine (ACh). The ACh interacts with the α7 Nicotine Receptor (CHRNA7) expressed by the macrophages, thus inducing down-regulation of pro-inflammatory cytokines.

Recent studies indicated that AChE inhibitors, widely used for the symptomatic treatment of Alzheimer’s disease and other dementias, can cause a significant modulation of innate immunity as a side effect.

In human, besides of CHRNA7, an isoform of the alpha7 nicotinic receptor can be transcribed by the CHRFAM7A gene. This gene is a hybrid product of a partial duplication and fusion of exons 5-10 of CHRNA7 gene with the novel FAM7A gene and maps 1.6 Mb apart from CHRNA7 in inverted orientation. The CHRFAM7A gene transcript undergoes alternative splicing, giving rise to two proteins of 46 and 35 KDa; the former differs from the α7 conventional subunit for the N-terminus domain, whereas the latter is a truncated form of the alpha7 subunit since it shares with CHRNA7 the four transmembrane domains, the cytoplasmic loop and the C-ter domain. These proteins seem to have a dominant negative effect on the conventional α7 function. Moreover, we have previously shown that CHRFAM7A is down-regulated upon LPS treatment in THP-1 cell model and primary monocytes and macrophages by a transcriptional mechanism reliant on NF-κB (Benfante et al., 2011).

In this work we explored the link between the “Cholinergic Anti-Inflammatory Pathway” and the AChEI Donepezil, by focusing on the regulation of CHRFAM7A and CHRNA7 expression in neuronal and immune cell models, to better understand their role in peripheral and central inflammation, and define a human restricted mechanism modulating the inflammatory response in neurodegenerative diseases.

Benfante et al. (2011) J Neuroimm. 230 (1-2), 74-84