AChE inhibitors as regulators of α7nAChR and its human-restricted duplicated isoform, CHRFAM7A, expression and modulation of the cholinergic anti-inflammatory pathway in AD

Neuroinflammation and cholinergic dysfunction, leading to cognitive impairment, are hallmarks of aging and neurodegenerative disorders, including Alzheimer’s disease (AD). Acetylcholinesterase inhibitors (AChEIs), the symptomatic therapy in AD, attenuate and delay the cognitive deficit by enhancing cholinergic synapses. The α7 nicotinic acetylcholine receptor (nAChR; CHRNA7) has shown a double-edged sword feature, as it binds with high affinity Aβ1–42, promoting intracellular accumulation and Aβ-induced tau phosphorylation, but also exerts neuroprotection by stimulating anti-apoptotic pathways. Moreover, it mediates peripheral and central anti-inflammatory response, being the effector player of the activation of the cholinergic anti-inflammatory pathway (CAIP), that, by decreasing the release of TNF-α, IL-1β, and IL-6, it may have a role in improving cognition. The finding in preclinical models that, in addition to their enzymatic function, AChEIs have neuroprotective properties mediated via α7nAChR and modulate innate immunity, possibly as a result of the increased availability of acetylcholine activating the CAIP, pave the way for new pharmacological intervention in AD and other neurological disorders that are characterized by neuroinflammation. CHRFAM7A is a human-specific gene acting as a dominant negative inhibitor of α7nAChR function, it is subject to copy number variation and present a polymorphism that leads to the production of a truncated protein. Recently it has been shown that CHRFAM7A mitigates Aβ1–42 internalization by α7nAChR, but its expression reduces the response to AChE inhibitors in AD patients, suggesting the gene-dosage of CHRFAM7A may explain the translational gap observed in AD therapy. Moreover, we have shown that donepezil modulates the expression of CHRNA7 and CHRFAM7A. The project aims to shed light on the effect of AChEi on the cholinergic anti-inflammatory pathway in AD, as the presence of the human-restricted CHRFAM7A gene might play a fundamental role in the regulation of CAIP and in the response to AChEI.

References:
3. Roberta Benfante, Ruth Adele Antonini, Maria De Pizzol, Cecilia Gotti, Francesco Clementi, Massimo Locati and Diego Fornasari – 2011 – Expression of the α7 nAChR subunit duplicate form (CHRFAM7A) is down-regulated in the monocytic cell line THP-1 on treatment with LPS. J Neuroimmunol 230: 74-84

Keywords: CHRNA7, CHRFAM7A, cholinergic anti-inflammatory pathway

Contacts: Roberta Benfante - e-mail: roberta.benfante@in.cnr.it

Website(s): www.in.cnr.it

Other: