The progress of the Pharmacological solutions in the Alzheimer disease

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Alzheimer's disease (AD) still represents the major socio-economic burden worldwide, with the potential to increase its prevalence in the near future. The worrying medical, social and economic scale of AD is in marked contrast to the lack of solutions available to efficiently tackle this major threat to individuals and society. Evidence has accumulated during the last 25 years indicating that AD is a disorder of protein aggregation in which two major components are concerned: β-amyloid peptide (Aß) produced by the sequential endoproteolysis of the amyloid precursor protein (APP), and Tau, a microtubule-associated protein. Alterations in the biogenesis of these proteins account for the main histological lesions that accumulate in the brain of AD patients, i.e. the senile plaques and the neurofibrillary tangles (NFT).

For many years, the core of the disease was constantly related to nerve-cell death induced by deposits of fibrillar Amyloid ß. This scenario is further complicated by the recent notion that Aß is present in several forms of aggregation possessing different capabilities of interfering with excitatory neurons. In particular, Aß oligomers have been described as the earliest effectors to negatively affect synaptic structure and plasticity. The production of Aβ is mediated by the concerted action of β-secretase (β-site APP Cleaving Enzyme, BACE1) and γ-secretase, a multimeric complex thought to be made up of an essential quartet of transmembrane proteins - presenilin 1 (PS1) or presenilin 2 (PS2), nicastrin, APH1, and PEN2. On the other hand, the main protagonist of the physiological APP metabolic pathway is α-secretase, which cleaves APP within the sequence corresponding to Aβ, thus preventing its formation.

For many years, Aß accumulation was considered the core of the disease and was constantly related to neuronal death induced by deposits of fibrillar Aß. This scenario has been recently complicated by the discovery of several Aß aggregation forms, each one with different capabilities of interfering with excitatory neurons. In particular, Aß oligomers have been described as the earliest effectors to negatively affect synaptic structure and plasticity.

Experiments in rodents support the notion that Aß impairs synaptic transmission and mouse models with increased production of these oligomers display cognitive impairment. In vitro studies demonstrated that Aß oligomers have an impact primarily on the postsynaptic compartment of the excitatory synapse. Oligomers, extracted from the cerebral cortex of AD patients, potently inhibited long-term potentiation, enhanced long-term depression and reduced dendritic spine density in rodent hippocampus.

Thus, despite many controversial, Aß remains as a key target for Alzheimer disease treatment, particularly for disease-modifying therapies aimed at therapies aimed at slowing or stopping the progression of the disease.