Alzheimer's disease

Alzheimer’s disease is a neurodegenerative disease characterized for a cognitive impairment and behavioural disturbances. This pathology is based on a progressive loss of cholinergic neurons in the hippocampus and the frontal cortex due to the presence of extracellular amyloid plaques of Aβ peptide and the intracellular neurofibrillary tangles made of tau protein. Aβ and tau induce inflammation, mitochondrial damage, acetylcholine decrease and oxidative stress and, the consequent neurodegeneration.

Cholinesterase inhibitors

- Block the acetylcholinesterase enzyme (AChE), which catalyzes acetylcholine (Ach) degradation. Additionally, acetylcholinesterase contains a peripheral locus that promotes Aβ aggregation. If both loci are inhibited, not only higher levels of Ach will be reached, but also Aβ aggregation will not be enhanced
- Show improvement in cognition
- Indirectly help function and behaviour
- Do not affect patient’s survival
- All AChE inhibitors have similar efficacy
- Generally well tolerated
- Cholinomimetic adverse effect, especially gastrointestinal
- Duration effect proved up to 12 months
- The combination treatment with memantine shows no additional clinical efficacy

Fig 2. Rivastigmine, donepezil and galantamine inhibit the acetylcholinesterase enzyme, thus, increasing the concentration of acetylcholine. Ach binds to muscarinic and nicotinic receptors decreasing the formation of Aβ peptide. mAChR also decreases the phospholipidation of tau, and nAChR enhances the formation of the soluble form of APP. Ach has anti-inflammatory effects by modulating the cytokine synthesis of the macrophages and other PBMC. Through all this effects, cholinesterase inhibitors improve cognitive outcomes. [2]

Conclusions

- Cholinesterase inhibitors only act on cholinergic symptoms. However, all disease-modifying drugs have failed clinical trials. Hence, nowadays there is not enough knowledge of the disease to be able to modify it.
- Cholinesterase inhibitors show a greater efficiency when administered in the earliest stages of the disease. One proposal has been to develop biomarkers available to detect Aβ peptide and hyperphosphorylated tau in the blood and the cerebrospinal fluid that could recognize the presence of Alzheimer’s disease when symptoms have not appeared yet. The main disadvantage of this approach is the economic cost of these biomarkers.
- Recently, the anti-inflammatory roll of cholinesterase inhibitors has also been elucidated, so α7-βAChR are considered a new therapeutic target.

Fig 3. Nowadays, disease-modifying drugs are being investigated. The image shows some of the most important disease-modifying drugs in study and the processes each one modulates.

References