

Cholinesterase inhibitors in the treatment of Alzheimer's disease

Laura Camps Cardenal
Universitat Autònoma de Barcelona (UAB), Bellaterra 2013

Alzheimer's disease

Alzheimer 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 A β peptide and the intracellular neurofibrillary tangles made of tau protein. A β and tau induce inflammation, mitochondrial damage, acetylcholine decrease and oxidative stress and, the consequent neurodegeneration.

Alzheimer's treatment

There is no current cure for Alzheimer's disease, though several symptomatic drugs are available. The cholinesterase inhibitors donepezil, rivastigmine and galantamine -together with memantine- are the only pharmacological treatment licensed for Alzheimer's disease.

The **aim** of this assay is to describe the anti-acetylcholinesterase drugs in the current context and their new applications. Certain disease-modifying drugs are detailed to understand why cholinesterase drugs and memantine are the only licensed ones.

Cholinesterase inhibitors

- Block the acetylcholinesterase enzyme (AChE), which catalyzes acetylcholine (ACh) degradation. Additionally, acetylcholinesterase contains a peripheral locus that promotes A β aggregation. If both locus are inhibited, not only higher levels of ACh will be reached, but also A β 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

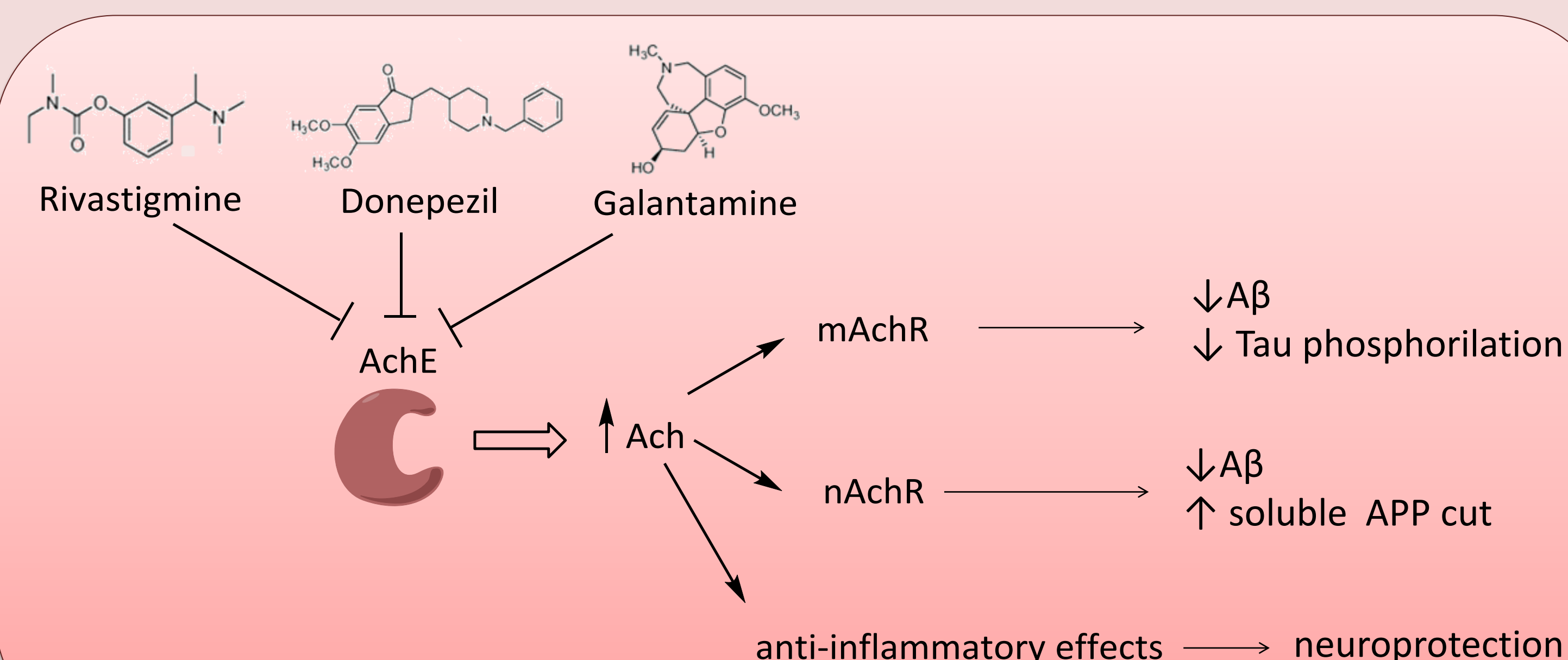


Fig 2. Rivastigmine, donepezil and galantamine inhibit the acetylcholinesterase enzyme, thus, increasing the concentration of acetylcholine. ACh binds to muscarinic and nicotinic receptors decreasing the formation of A β peptide. mAChR also decreases the phosphorylation of tau, and nAChR enhances the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

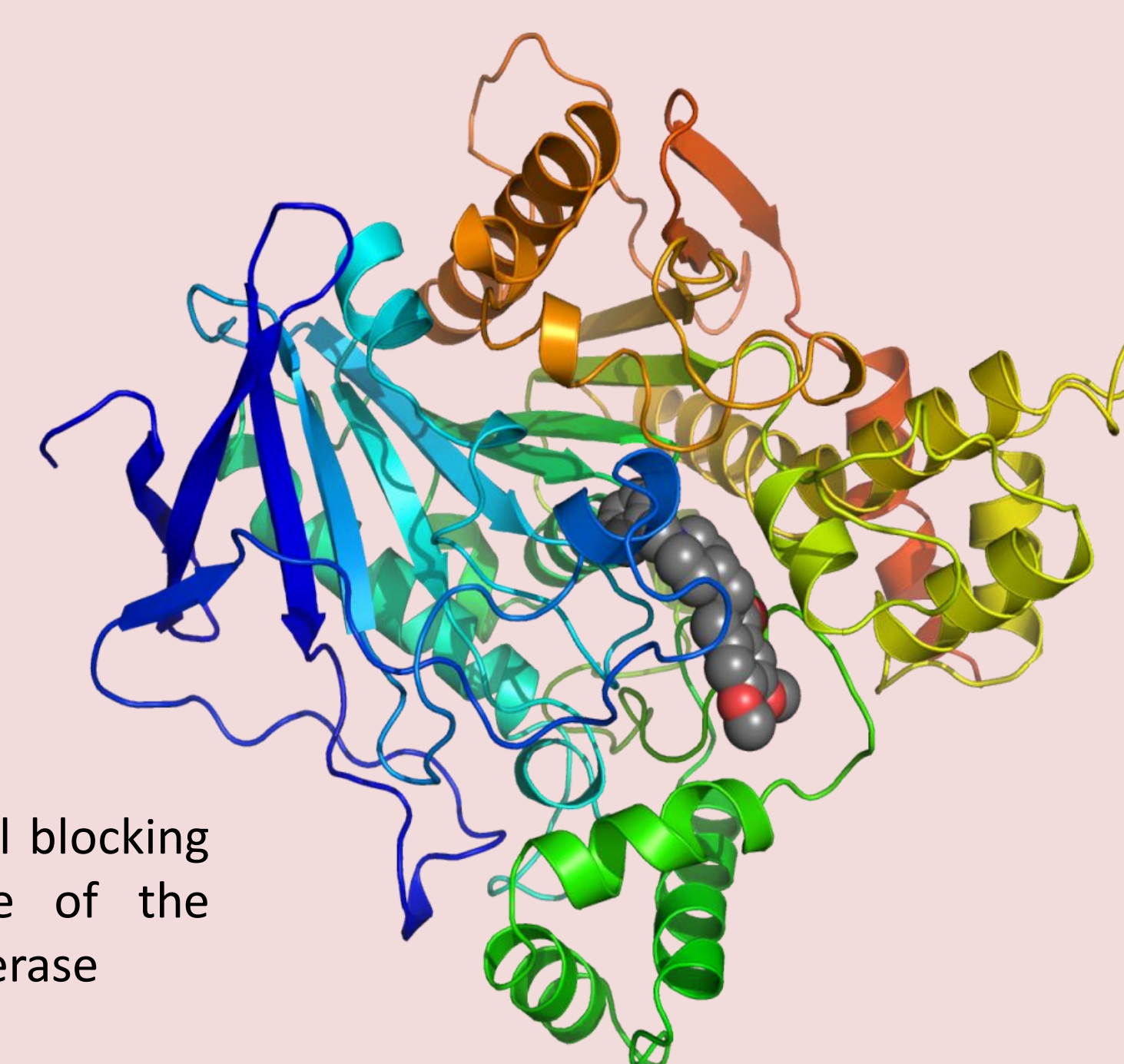


Fig 1. Donepezil blocking the active site of the acetylcholinesterase enzyme. [1]

Donepezil

- Second-generation reversible cholinesterase inhibitor
- Specific acetylcholinesterase enzyme inhibition
- Anti-inflammatory effect: ACh can inhibit the synthesis of the pro-inflammatory cytokines in the macrophages cells

Galantamine

- Competitive and reversible cholinesterase inhibitor
- Specific acetylcholinesterase enzyme inhibition
- Allosteric modulation of nicotinic ACh receptors in the brain

Rivastigmine

- Pseudo-irreversible cholinesterase enzyme
- Non-specific inhibition since it blocks both butyrylcholinesterase and acetylcholinesterase enzymes. Non-selective inhibition is associated with peripheral side effects

Other pharmacological approaches

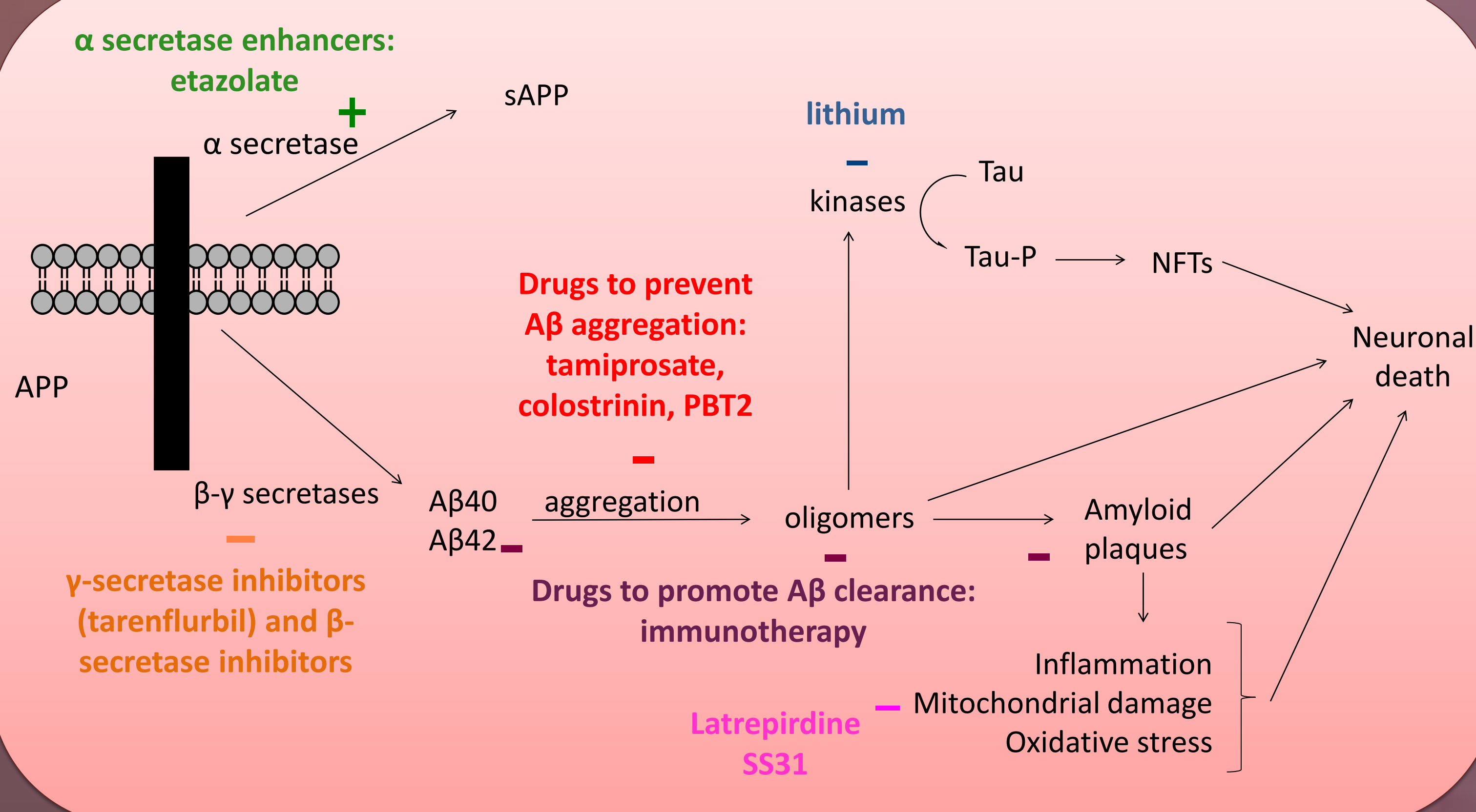


Fig 3. Nowadays, disease-modifying drugs are being investigated. The image shows some of the most important disease-modifying drugs in study and the processes each one modulates.

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 A β 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 α 7-nAChR are considered a new therapeutic target.

References

- [1]. Kryger G, Silman I, et al. Structure of acetylcholinesterase complexed with E2020 (Aricept): implications for the design of new anti-Alzheimer drugs". 1999; vol 7 (3): 297-307
- [2]. Luo W, Li Y-P, et al. Design, synthesis and evaluation of novel tacrine-multialkoxybenzene hybrids as dual inhibitors for cholinesterases and amyloid beta aggregation. Elsevier. 2011; vol 19 (2): 763-770
- [3]. Ballard C, Gauthier S, et al. Alzheimer's disease. Lancet. 2011; vol 377: 1019-1031
- [4]. NHS (National Institute for Health and Clinical Excellence); April 2013 [cited May 2013]. Quick reference guide: Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease
- [5]. Bencherif M, Lippiello PM, et al. Alpha7 nicotinic receptor as novel therapeutic targets for inflammation-based diseases. Cell and Molecular Life Sciences. 2010; vol 68: 931-949
- [6]. Galimberti D, Scarpini E. Progress in Alzheimer' disease. Springer-Verlag. 2011; vol 259: 201-211