NEW THERAPEUTIC STRATEGIES FOR ALZHEIMER'S DISEASE:
NEW TREATMENTS AGAINST BETA-AMYLOID AND TAU-PROTEIN

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Alzheimer's disease (AD) is the most common cause of dementia (more than 50% of all the cases), affecting up to 8 % of the elderly population worldwide. It is considered to be the most frequent neurodegenerative disease. It has been demonstrated that the disease initiates with the early accumulation of ß-Amyloid at the preclinical stage in the neocortex and subsequently Tau-protein accumulation, inflammatory process and cognitive disturbances appear [1].

OBJECTIVES

- To expound how some proteins are involved in the development of the disease and which mechanism is followed.
- To show new drugs that have been tested in clinical trials, how they act and the results obtained in the studies.

Keywords: *Alzheimer's Disease, AD, ß-Amyloid (Aß), Tau-protein, aggregation, therapeutic strategies*

ß-Amyloid

ß-Amyloid peptide is a product of cleavage of a precursor protein (APP). First, it can be cleaved by two secretases: α- and ß-secretase. Depending on the secretase involved in the cleavage the process will be Non-Amyloidogenic or Amyloidogenic.

Later, Amyloid precursor protein is cleaved by a γ-secretase. Amyloidogenic products can be misfolded and form harmful aggregates, leading to cell death and inflammation [2].

Normal Amyloid precursor protein → **ß- and γ-secretase cleavage** → **Aß peptide monomers** → **Harmful aggregation in extracelular space**

Tau-protein

Tau-protein promotes tubulin polymerization. It is a microtubule-associated Tau-protein (MAPT) mainly found in axons and stimulates the assembling of microtubules.

In a healthy brain, 2 or 3 residues on tau are phosphorylated. In contrast, in Alzheimer's disease and other tauopathies, there is a hyperphosphorylation in different residues.

Moreover, hyperphosphorylation stimulates fibrillization and aggregation into neurofibrillary tangles (NFT) [2].

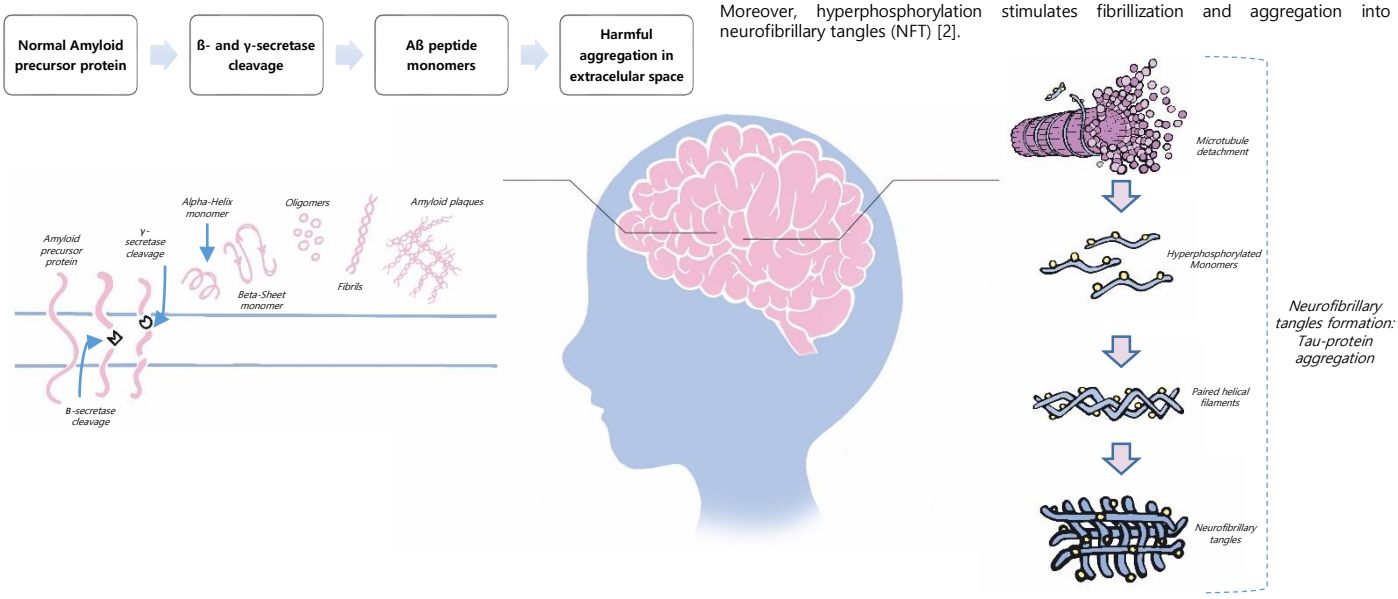

Figure 1. Aggregation and accumulation of ß-Amyloid and Tau-protein in the brain. On the left, it can be observed how ß- and γ-secretases cleave APP, leading to ß-Amyloid formation. On the right, there is a scheme of neurofibrillary tangles formation.

Novel therapeutic strategies

Against β-Amyloid

Immunotherapy. It can be directed against APP, monomeric Aß, soluble oligomers, insoluble fibrils and carrier proteins.

- *Active immunization*. Prolonged antibody response using a small number of vaccinations. Example: ACCD-001 that contained a six amino acid sequence $Aß_{1-6}$ with a surface-active saponin-adjuvant QS-21. Phase II trials showed adverse effects.
- *Passive immunization*. Antibodies delivery from the patient's own immune system, humanized murine monoclonal antibodies or human donors of polyclonal antibodies. Example: Solanezeumab, a monoclonal antibody that binds specifically to the mid-domain of Aß ($Aß_{16-24}$). Positive therapeutic effects at an early stage were obtained [3].

Against γ- and β-secretases

- **γ-secretase inhibitors (GSIs).** GSIs are capable of inhibiting the cleavage of ß-Amyloid protein (Beta-Amyloid production inhibitors). Example: ELND006 that was removed at an early stage because induced noticeable side effects [4].
- **γ-secretase modulators**. Regulate the functionality of γ-secretase. Example: Avagacestat interacts with shorter forms of Beta-Amyloid and alters the proteolytic activity of the protease without affecting Notch protein transformation [1].
- **ß–secretase inhibitors.** Small molecule inhibitors. Interfere with the amyloid formation pathway. Example: MK-8931 has shown dosage-dependent reduction in the level of Beta-Amyloid in the cerebrospinal fluid in more than 80% of patients [1].

Against Tau-protein

- **Immunotherapy**. Intends to prevent formation of neurofibrillary tangles. It has been found that antibodies against Tau-protein can bound to pathological Tau-proteins. Some vaccines have been developed. Example: ACI-35, an example for active immunization tested in mild-to-moderate AD patients. Otherwise, passive immunization appears to show less side effects [5].
- **Hindering phosphorylation of Tau-Protein to prevent aggregation.** It appears to be a bright strategy for the treatment of AD, even in the symptomatic phase of the disease. Example: LMTX showed prevention of Tau interactions, an increment in clearance of Tau from the brain and anti-β-Amyloid aggregation activity [1,5].

CONCLUSIONS

- Although there have been several clinical trials, most phase II trials with positive results do not succeed in phase III and show either adverse effects or lack of therapeutic efficacy.
- Even though there are still studies focused on Aß protein, novel therapies are now directed against other proteins involved in the progression of the disease, for instance, Tau protein or secretase inhibitors. These strategies seem to be promising and may be the answer to cure Alzheimer's disease.
- In conclusion, better knowledge of the disease and the outcome of useful and potent biomarkers will lead to the development of an effective drug.

References: **1.** J. Godyń, J. Jończyk, D. Panek, and B. Malawska, "Therapeutic strategies for Alzheimer's disease in clinical trials," *Pharmacol. Reports*, vol. 68, no. 1, pp. 127–138, 2016. **2.** O. G. Tatarnikova, M. A. Orlov, and N. V. Bobkova, "Beta-Amyloid and Tau-Protein: Structure, Interaction, and Prion-Like Properties," *Biochem.*, vol. 80, no. 13, pp. 1800–1819, 2015. **3.** L. Lannfelt, N. R. Relkin, and E. R. Siemers, "Amyloid-ß-directed immunotherapy for Alzheimer's disease," *J. Intern. Med.*, vol. 275, no. 3, pp. 284–295, 2014. **4.** T. E. Golde, E. H. Koo, K. M. Felsenstein, B. A. Osborne, and L. Miele, "γ-Secretase inhibitors and modulators," *Biochim. Biophys. Acta - Biomembr.*, vol. 1828, no. 12, pp. 2898–2907, 2013. **5.** H. Coman and B. Nemeș, "New Therapeutic Targets in Alzheimer's Disease," *Int. J. Gerontol.*, vol. 11, no. 1, pp. 2–6, 2017.

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