# ALZHEIMER'S DISEASE

## Β-AMYLOID PEPTIDE AGGREGATION AND ENDOGENOUS ELIMINATION

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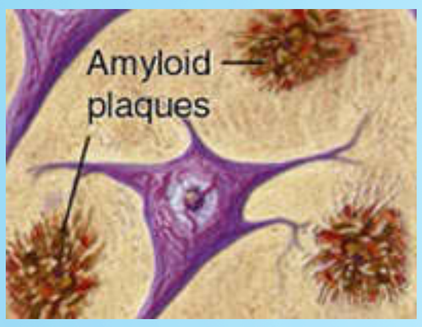
## INTRODUCTION

Alzheimer's disease (AD) is the most common form of senile dementia that affects more than 30 million individuals worldwide. It is a degenerative neurological disorder characterized by gradual memory loss, cognitive impairments and deterioration of language skills.




**Sporadic Alzheimer's disease:** The disease can affect adults at any age, but usually occurs after age 65. It is associated with the presence of the apolipoprotein E (APOE) ε4 allele.

**Familial Alzheimer's disease**: The disease runs in a few families and is very rare. It has been linked with mutations in APP, PSEN1 and PSEN2 genes. No treatment can stop the disease. However, some drugs may help keep symptoms from getting worse for a limited time (1).

## Endogenous elimination

There are two major pathways by which Aß is cleared from the brain: receptor-mediated clearance by cells in the brain parenchyma (microglia, astrocytes and neurons), along the interstitial fluid drainage pathway or through the BBB; and through endopeptidase- mediated proteolytic degradation.

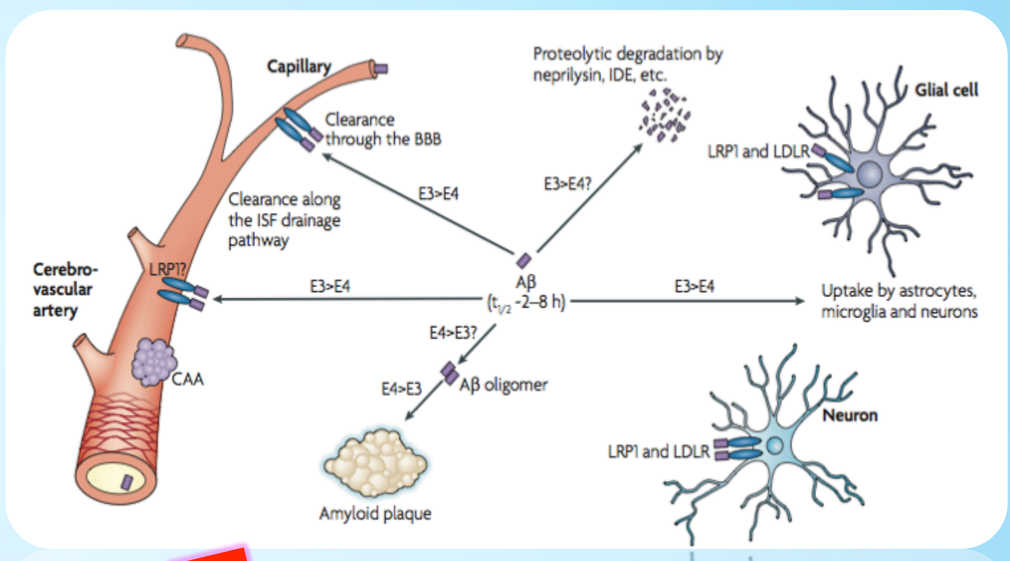


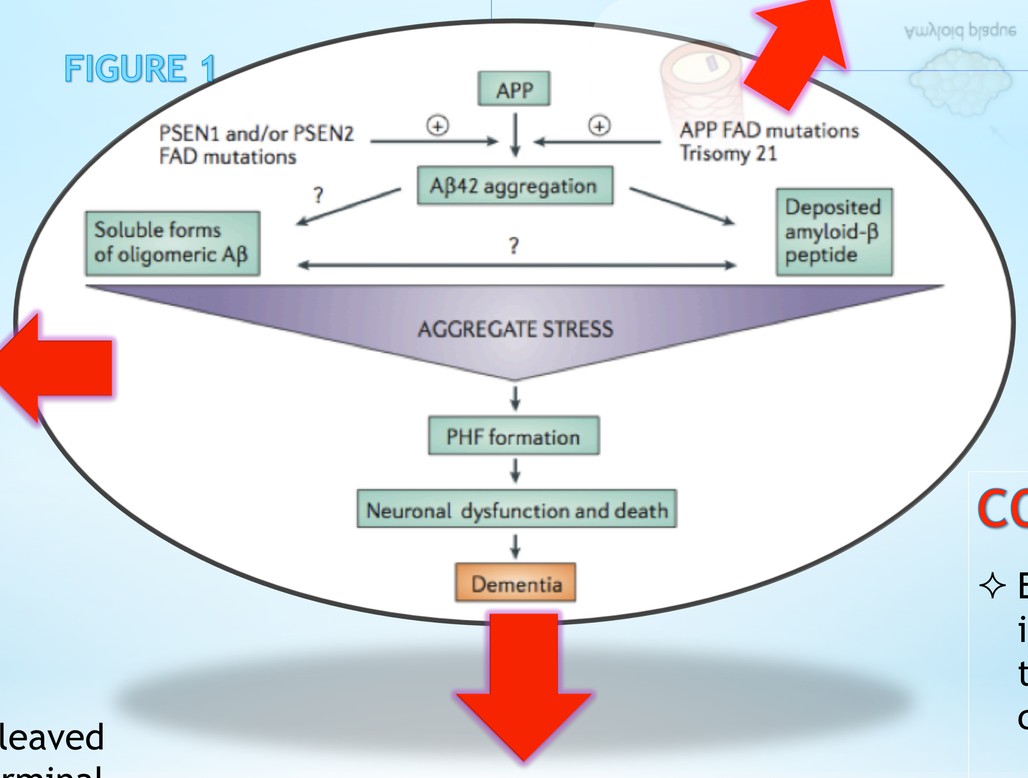

FIGURE 4 (3)

## Amyloid cascade hypothesis

The protein implicated in development of Alzheimer's disease is APP.

The amyloid cascade hypothesis posits that the deposition of the amyloid-ß peptide in the brain parenchyma initiates a sequence of events that ultimately lead to AD dementia. Autosomal dominant mutation that cause early onset familial Alzheimer's disease (FAD) occur in three genes: PSEN1, PSEN2 and APP.

FIGURE 1




## APP processing

In the non-plaque-forming pathway, APP is cleaved first by α-secretase to yield a soluble N-terminal fragment (sAPPα) and a C-terminal fragment (CTFα). CTFα is retained in the membrane, where it is acted upon by presenilin-containing α-secretase to yield a soluble N-terminal fragment (p3) and a membrane-bound C-terminal fragment (AICD, or APP intracellular domain).

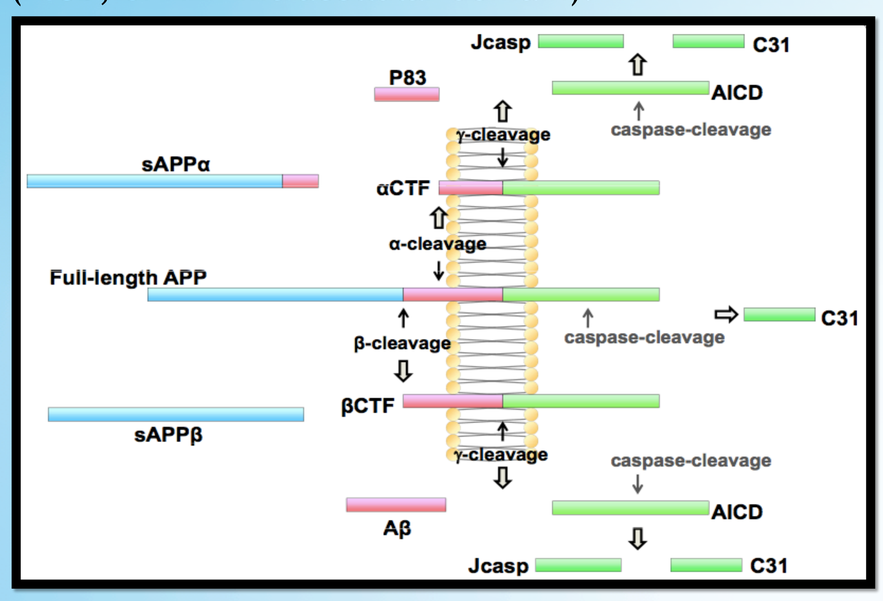



FIGURE 2 (2)

In the plaque-forming pathway, APP is cleaved first by a different enzyme, ß-secretase (BACE1). APP is cleaved, yielding a soluble N-terminal fragment (sAPPß) and a membrane-bound C-terminal fragment (CTFß). CTFß is then acted upon by δ-secretase, yielding a membrane-bound C- terminal fragment (AICD) the same as before, and a soluble N-terminal fragment (amyloid-ß, or Aß) that is longer than p3.

## AD diagnosis and therapy

Current symptomatic therapies for AD include the:

- ✧ acetylcholinesterase inhibitors (donepezil (Aricept; Eisai/Pfizer).
- ✧ galantamine (Razadyne; Johnson & Johnson) and rivastigminine (Exelon; Novartis).
- ✧ a low-affinity NMDA (N-methyl-D-aspartate) receptor antagonist (memantine) for

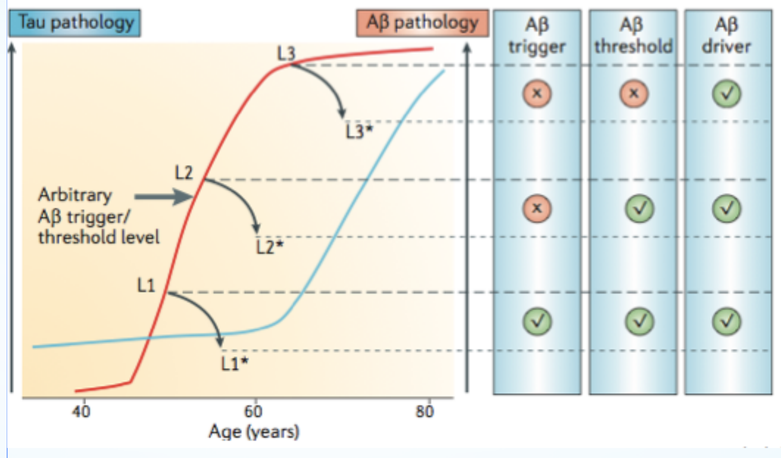



FIGURE 3

Potential amyloid-ß scenarios and treatment.
If the amyloid-ß trigger scenario is true, then a therapeutic agent would have no efficacy if it is administered after some amyloid-ß deposition has occurred and aggregate stress has triggered the disease process, even if the therapeutic was eventually able to lower the levels of deposited amyloid-ß to below the original trigger point.

## CONCLUSION

- ✧ Elucidation of APP metabolism will be important for identifying new potential therapies to reduce Aß accumulation and combat AD.
- ✧ LRP1 has a major role in regulating brain and systemic clearance of Alzheimer's Aß.
- ✧ LRP2 plays a potential key role in the pathogenesis of AD.
- ✧ Therapeutic success may occur relatively soon.

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