# Causality of Alzheimer's Disease: Theory and Mouse Models

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## Introduction: Alzheimer's Disease (AD)

- Neurodegenerative disorder that manifests clinically as early loss of episodic memory, progressing to other cognitive domains.
- Histopathological hallmarks: senile plaques (formed by the amyloid beta – Aβ – peptide) and neurofibrillary tangles (composed by aberrant, hyperphosphorylated tau protein).
- The underlying mechanisms causing the dementia are unknown.

## Aims

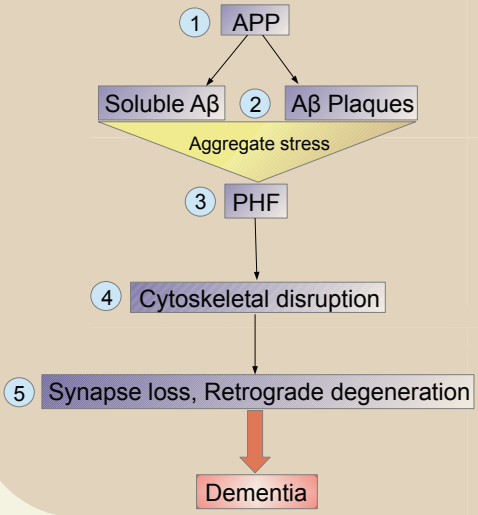
To review data obtained from transgenic mice, to provide an insight into:

- Pathogenesis of AD
- Identifying possible therapeutic targets

## Materials & Methods

- Research in the Pubmed and ScienceDirect databases.
- Keywords used: "Alzheimer", "amyloid", "tau", "secretase", "mouse", "model".
- 60 articles from 1990-2013 collected. 29 papers included in the bibliography.

## The Amyloid Cascade Hypothesis




**1**. APP Sequential cleavage by β- and γ- secretases leads to the production of the Aβ peptide, which varies in length (major forms are 40 and 42 amino acids).

**2**. The neurotoxicity of Aβ might be due to its soluble or oligomeric forms. By unknown mechanisms, the effect of Aβ peptide leads to an eventual hyperphosphorylation of Tau protein, the physiological role of which is to stabilize tubulin monomers.

**3**. Tau is hyperphosphorylated by kinases (such as MAP-Kinase, CSK3, Cdk5), which promotes its separation from microtubules and aggregation in Paired Helical Filaments (PHF). Calcineurin and Phosphatase Protein 2A can dephosphorylate Tau.

**4**. Without Tau, microtubules cannot maintain their physiological structure and tubulin units disassemble.

**5**. Axonal structure is compromised, which ultimately causes the breakage of synapses. Neurons then degenerate and die.

## APP mutations in Familial Alzheimer's Disease

Mutations in APP associated to familial AD are used in mouse models. Each presents different features in the disease:

***Swedish*** → Enhances β-secretase processing

***Flemish*** → Decreases α-secretase cleavage

***Dutch, Arctic, Iowa*** → Increase aggregation

***Indiana, London, Florida*** → Increase Aβ42/Aβ40

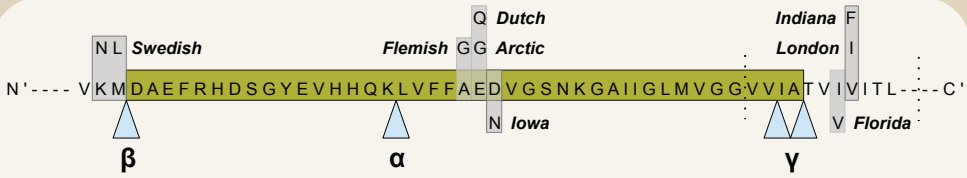



***Figure 1***. APP mutations related to familial Alzheimer's disease that are used in mouse models. The Aβ fraction is highlighted in green. The vertical dotted lines enclose the membrane domain, and the β, α and γ cleavage sites are represented with triangles.

## Transgenic Mice Generation

*Methods:*

1. ***Pronuclear Injection***: Gene injected in a 1-cell embryo (pronuclear phase). Outcome: Random insertion, overexpression, temporal and spatial misexpressions.
2. ***Gene Targeting***: Injection of a modified endogenous gene in Embryonic Stem cells. Outcome: Normal expression.

*Mutations Used in AD mouse models:*

- APP
- Presenilins
- Tau

*Different combinations allow the study of different components of the disease*

| Mouse Model | Gene (Mutation) | Intra-neuronal Aβ | Parenchymal Aβ plaques | Hyperphos-phorylated Tau | Neuro-fibrillary tangles | Neuronal loss | Synaptic loss | CAA |
|---|---|---|---|---|---|---|---|---|
| PDAPP | APP (V717F) | - | Yes | Yes | No | No | Yes | - |
| Tg2576 | APP (K670N/M671L) | Yes | Yes | - | - | No | No | - |
| TgCRND8 | APP (K670/M671L,V717F) | - | Yes | - | No | No | - | - |
| APP/PS1 | APP (K670N/M671L), PS1 (M146L) | - | Yes | - | - | - | - | - |
| APP23 | APP (K670N/M671L) | - | Yes | Yes | No | Little | Yes | Yes |
| Tg-SwDI | APP (E693Q,D694N) | - | Yes | - | - | - | - | Yes |
| APPDutch | APP (E693Q) | - | Little | - | - | - | - | Yes |
| APPDutch/PS1 | APP (E693Q), PS1 (G384A) | - | Yes | - | - | - | - | Little |
| hAPP-Arc | APP (E693G,K670N/M671L,V717F) | - | Yes | - | - | - | - | Little |
| Tg-ArcSwe | APP (E693G,K670N/M671L) | Yes | Yes | - | - | - | - | Yes |
| APPArc | APP (E693G) | - | Yes | - | - | - | - | Yes |
| TAPP | APP (K670N/M671L), Tau (P301L) | - | Yes | - | Yes | - | - | - |
| 3xTg-AD | APP (K670N/M671L), Tau (P301L) | Yes | Yes | Yes | Yes | - | No | - |
| $APP_{SL}$/PS1 | APP (K670N/M671L,V717I), PS1 (M233T/L235P) | Yes | Yes | - | - | Yes | Yes | - |
| APP/PS1KI | APP (K670N/M671L,V717I), PS1 (M233T/L235P) | Yes | Yes | - | - | Yes | Yes | - |
| 5xFAD | APP (K670N/M671L,I716V,V717I), PS1 (M146L/L286V) | Yes | Yes | - | - | Yes | Yes | - |

***Figure 2***. Pathological features of several mouse models. CAA: Cerebral Amyloid Angiopathy; bar (-): not reported

## Relevant Findings in Transgenic Mice

- Mice lacking APP show impaired memory
- Mice lacking β-secretase seem cognitively normal
- APP transgenic mice lacking β-secretase do not generate Aβ plaques
- Low metabolism accompanies high β-secretase activity
- Aβ42 fibrils injection leads to 5-fold increase in neurofibrillary tangles
- Aβ monoclonal antibodies rapidly revert memory deficits, without reducing plaque burden

## Conclusions

Aβ triggers the neurodegeneration mechanisms

Low neuronal metabolism accompanies Aβ production

APP seems to have a physiological role, thus its supression is not a therapeutical target

Beta-secretase inhibition or Aβ removal are promising therapeutic strategies