BRINGING TOGETHER THE PIECES OF AMYLOID HYPOTHESIS

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Alzheimer's disease and the amyloid hypothesis:

Alzheimer's disease is the main cause of dementia, leading to deteriorated cognitive, functional and behavioural capabilities. There are two types of Alzheimer's:
-**Early-onset Alzheimer disease**: appears in young individuals (40-50) by autosomic dominant mutations in *APP*, *PSEN1* or *PSEN2*.
-**Late-onset Alzheimer disease**: affects individuals older than 65 and is not genetic. It seems to be a consequence of a decreased clearance of Aβ.

The main alterations in the brain are intracellular **neurofibrillary tangles** (NFTs) of hyperphosphorilated tau and extracellular **amyloid β plaques**, with neuronal loss and activated glia. Lesions on the temporal lobe are critical as it is associated with memory and cognition. The isolation and sequentiation of amyloid β peptide (Aβ) in patients suffering from Alzheimer and Down's syndrome by Glenner and Wong led to the amyloid hypothesis, which established that Aβ elevations underlie the origin of the disease. Recently, the **peripheral sink** hypothesis, which postulates that Aβ exists in an equilibrium between brain and periphery, has given new insights in the therapeutics and pathoetiology of Alzheimer.

Aβ production and Homeostasis:

Amyloid **homeostasis** in the interstitial fluid is controlled by:
- ✓amyloid production from APP
- ✓protease elimination
- ✓transport through the blood-brain-barrier
- ✓aggregation and binding to plasma proteins
- ✓ bulk flow elimination through the cerebrospinal fluid

→ **Late-onset Alzheimer's disease**

APP (Amyloid Precursor Protein) is a transmembranal protein type I that can be processed by two pathways:
-Cleavage by α-secretase (ADAM/BACE2) and γ-secretase that blocks Aβ production cutting the Aβ domain
-Cleavage by β-secretase (BACE1) and γ-secretase that produces Aβ: Aβ40 and Aβ42 (more fibrillogenic)
Y-secretase is a complex with aph-1a, aph-1b, pen-2, nicastrin and presenilins 1/2 (PSEN1/2).

Arguments of the hypothesis:

- All individuals affected by Down's syndrome (trisomy 21) suffer from Alzheimer and *APP* has been mapped to chromosome 21
- Mutations associated with early-onset Alzheimer (*APP*, *PSEN1/2*) elevate Aβ levels
- Mice overexpressing *APP* with knockout *BACE1* show neither memory deficits nor amyloid plaques
- Parenteral administration of α-Aβ produces an Aβ40 and Aβ42 increase in blood that correlates to hippocampal and cortical Aβ burden
- Alzheimer's symptoms are alleviated by immunization with α-Aβ or sLRP that reduces plaque burden
- Tau mutations cause frontotemporal dementia without amyloid plaques and tau is apparently a consequence of Aβ
- Worster-Drought syndrome is caused by amyloid deposition and generates NFTs and neuronal loss

Neurotoxicity of amyloid β peptide:

The neurotoxic species are **Aβ oligomers**, which correlate better with the severity of the disease and when purified and injected in rats block long-term potentiation and increase errors in cognitive tests.
Toxicity in neurons could be mediated by:
-Binding to receptors
-Non-specific alterations, such as calcium homeostasis disruption and oxidative stress.

There is also implication of astrocytes (which decrease amyloid burden) and microglia (production of cytokines).
These alterations would precede neuronal loss by **apoptosis** (neurons show upregulation of Bax, activated caspase-3 and down-regulation of Bcl-2), but there is also evidence of necrosis.

Controversies of the hypothesis:

- NFTs and neuropil threads precede amyloid plaques (but it could not be assessed whether patients were in pre-dementia state)
- Amyloid plaque burden does not correlate with the severity of the disease
- Bapineuzumab trials decreased plaque burden without cognitive improvement (maybe due to late administration)
- *APP*, *PSEN1* and *PSEN2* mutations elevate Aβ levels without correlation with Alzheimer's onset age
- Transgenic mice with Aβ deposition do not show clear neuronal loss, but some tau pathologies do.

Two new hypothesis:
✓**Presenilin hypothesis**: relaxed specificity of γ-secretase allows it to act upon other substrates, which would be the cause of the disease
✓**Dual hypothesis**: there is a pathogenic initiator upstream tau and amyloid alterations (apoE, GSK3, retromer)

The proteolitic clearance model:

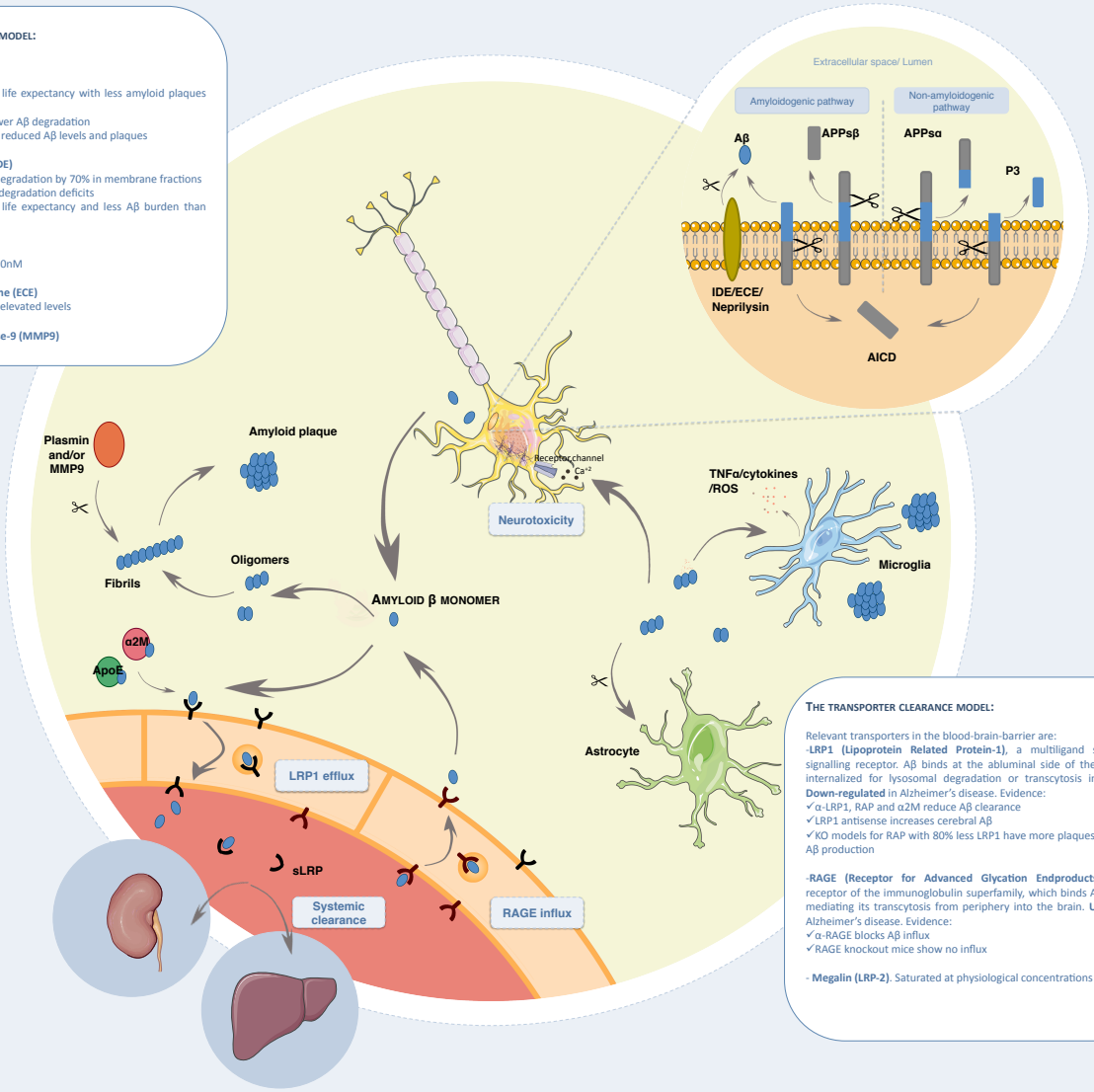
The main proteases are:
-**Neprilysin**:
✓NEPxAPP mice have higher life expectancy with less amyloid plaques and Aβ levels than APP mice
✓NEP knockout mice have lower Aβ degradation
✓Lentiviral expression of NEP reduced Aβ levels and plaques

-**Insulin-degrading enzyme (IDE)**
✓IDE inhibitors decrease Aβ degradation by 70% in membrane fractions
✓IDE knockout mice have Aβ degradation deficits
✓IDExAPP mice have higher life expectancy and less Aβ burden than APP mice

-**Plasmin**
✓Degrades fibrillar Aβ at 10-30nM

-**Endothelin-converting enzyme (ECE)**
✓ECE knockout mice have Aβ elevated levels

-**Matrix metalloendopeptidase-9 (MMP9)**
✓Degrades fibrillar Aβ



The transporter clearance model:

Relevant transporters in the blood-brain-barrier are:
-**LRP1 (Lipoprotein Related Protein-1)**, a multiligand scavenger and signalling receptor. Aβ binds at the abluminal side of the BBB and it is internalized for lysosomal degradation or transcytosis into the blood. **Down-regulated** in Alzheimer's disease. Evidence:
✓α-LRP1, RAP and α2M reduce Aβ clearance
✓LRP1 antisense increases cerebral Aβ
✓KO models for RAP with 80% less LRP1 have more plaques with the same Aβ production

-**RAGE (Receptor for Advanced Glycation Endproducts)**, multiligand receptor of the immunoglobulin superfamily, which binds Aβ at nM levels mediating its transcytosis from periphery into the brain. **Up-regulated** in Alzheimer's disease. Evidence:
✓α-RAGE blocks Aβ influx
✓RAGE knockout mice show no influx

- **Megalin (LRP-2)**. Saturated at physiological concentrations with ApoJ.