Neuroinflammation in Alzheimer's disease

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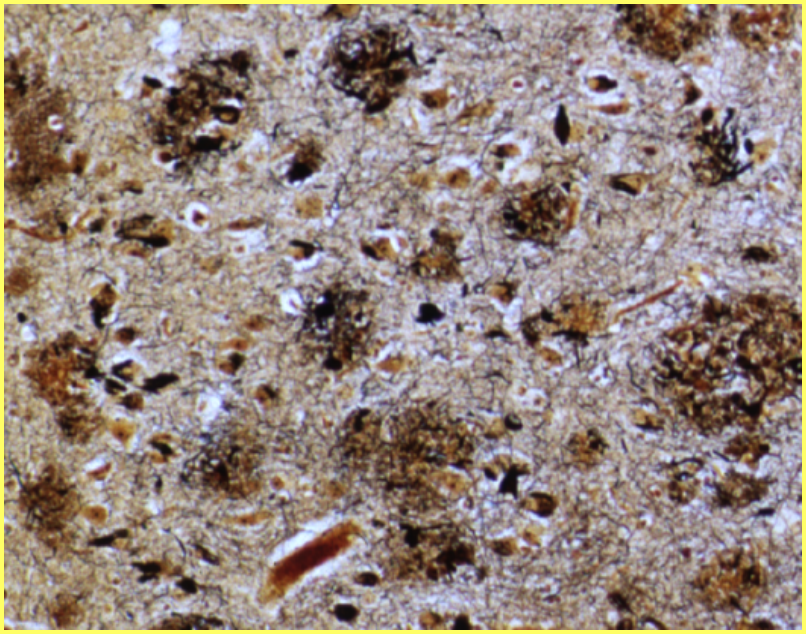
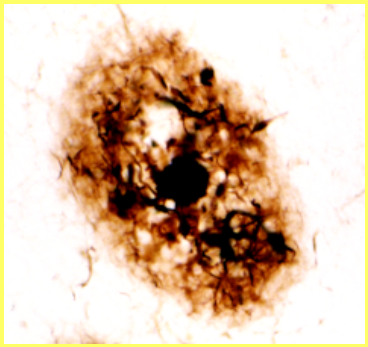
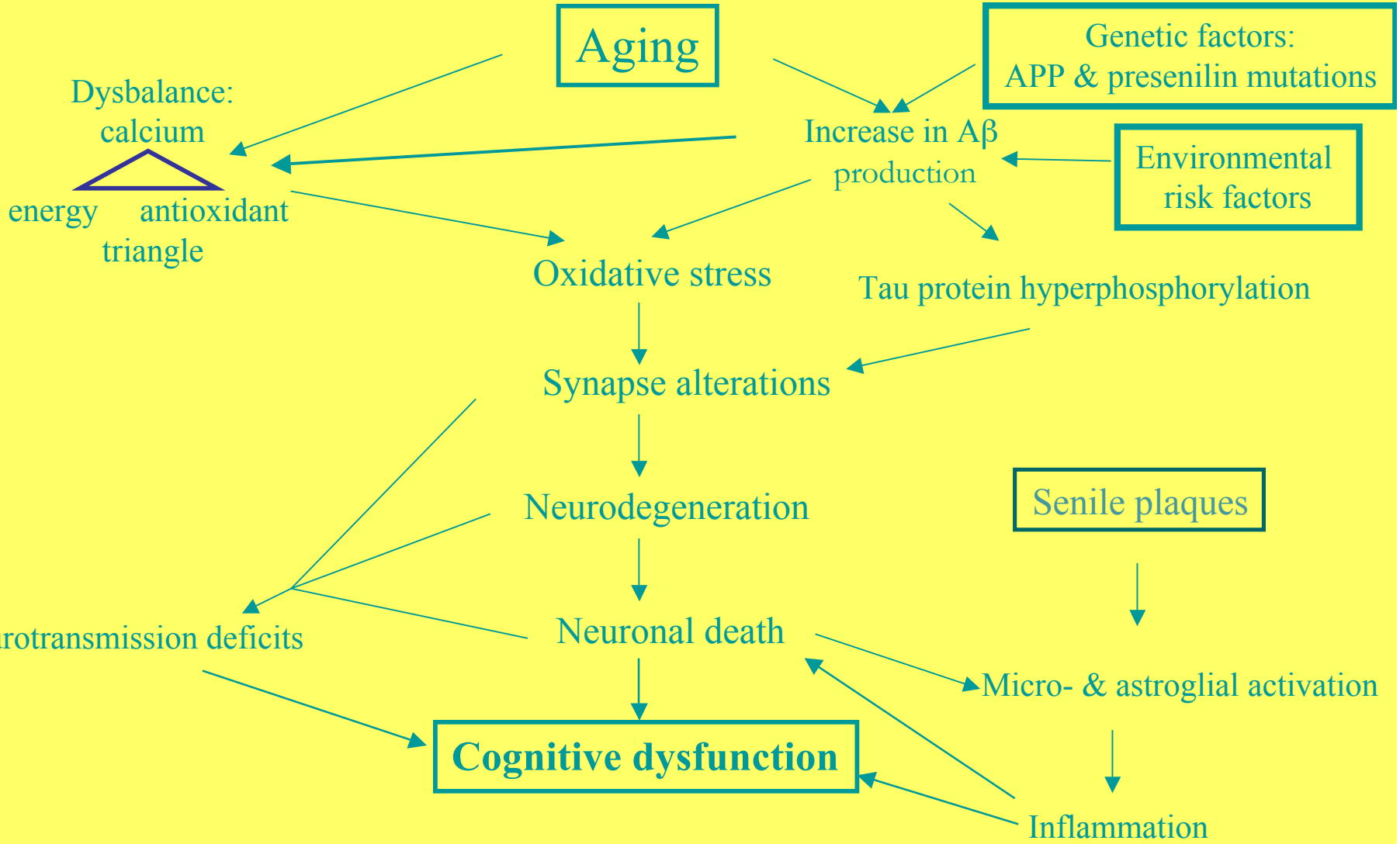
AD pathological hallmarks





Courtesy of Nenad Bogdanovici, KI

Pathogenic processes leading to Alzheimer's disease *Possible therapeutical targets*



Adapted after Bengt Winblad

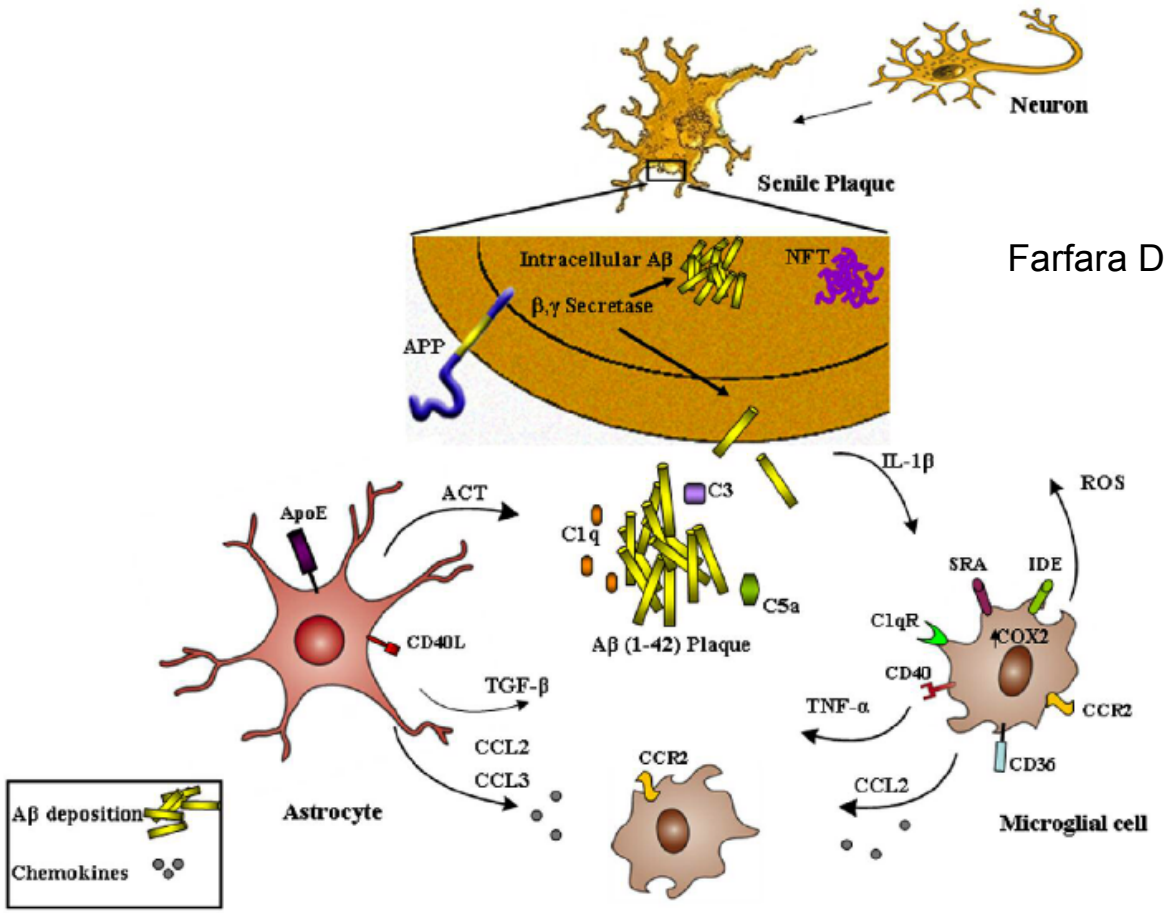
Amyloid (starch, amyleum)deposits - plaques

Composed of

- Beta-amyloid
- Ferritin
- **Components of the complement pathway**
- Alpha1-chemotrypsin
- Alpha2-macroglobulin
- LDL receptor related protein
- APP
- Acethylcholinesterase
- Glycosaminoglycans
- Apolipoprotein E, etc.

In contact with

- **Activated microglia** (adiacent to the central amyloid core of the neuritic plaque)
- Surrounding **reactive astrocytes** (with abundand glial filaments)



Farfara D et al, J Cell Mol Med, 2008

Figure 1. Activation of the glial cell response toward the formation of senile plaque in Alzheimer's disease. The overproduction and extracellular deposition of amyloid β-peptide (AAβP) and an intracellular deposition of neurofibrillary tangles (NFT) initiates the pathogenesis of AD. The production of complement components (C1q, C3, and C5) is the first stage in response to Aβ deposition, resulting in the attraction and activation of microglial cells. Both microglial cells and astrocytes produce multiple proinflammatory and neurotoxic factors: transforming growth factor (TGF)-1; tumor necrosis factor (TNF)-α; interleukin-1 (IL-1); CC-chemokine ligand (CCL); antichymotrypsin (ACT); reactive oxygen species (ROS); and cyclooxygenase 2 (COX2). Activated microglial cells express various scavenger receptors (SRs) that mediate phagocytosis of Aβ, such as CD36, SR-A. Microglial cells can also degrade Aβ by releasing Aβ-degrading enzymes, such as insulin-degrading enzyme (IDE).

Immune response in AD brain

- Serum and CSF from AD patients contain ab that recognize human senile plaques[1]
- Highly conserved receptors on microglia and glial cells (complement R, Toll-like R, scavanger R)
- Complement system is synthetized by astrocytes, microglia and neurons and is activated by beta-amyloid (C1q)
- C1q mRNA in AD hippocampus – increased 80 times compared to control

1 - Gaskin et al., J Exp Med, 177, 1993
2 – Yasojima et al., Am J Pathol, 154, 1999

Immune response in AD brain

- Absence of C1q in AD transgenics leads to less neuropathology[1]
- Activation of complement – dual role:
  - Leads to activation of glial cells – inflammatory events – neuronal dysfunction and degeneration (through inflammatory cytokines, ROS, NO, etc.)
  - Useful for elimination of aggregated and toxic proteins (phagocytosis of beta-amyloid by microglia)

1- Fonseca et al., J Neurosci, 24, 2004

Microglial cells in AD

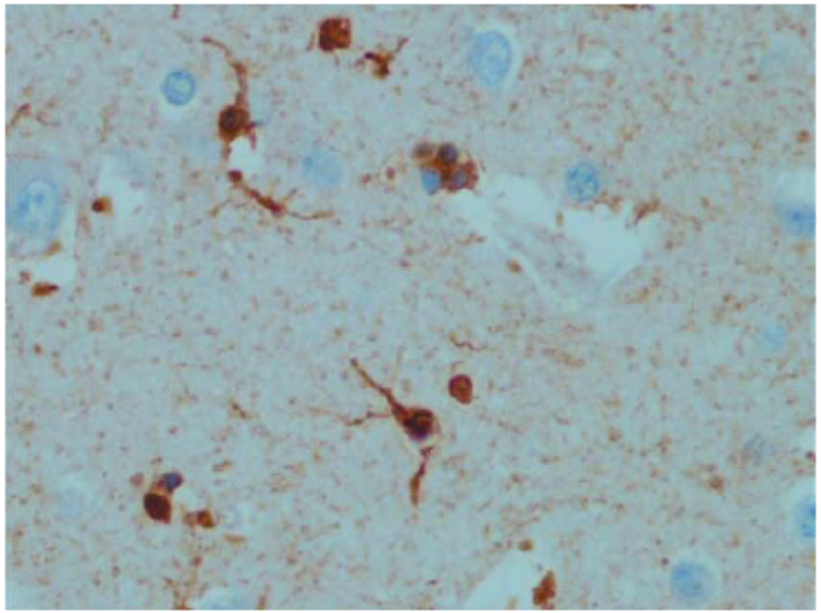


Fig. 1. Alzheimer's disease. Immunohistochemical reaction of microglial cells to antibody against ferritine, x400

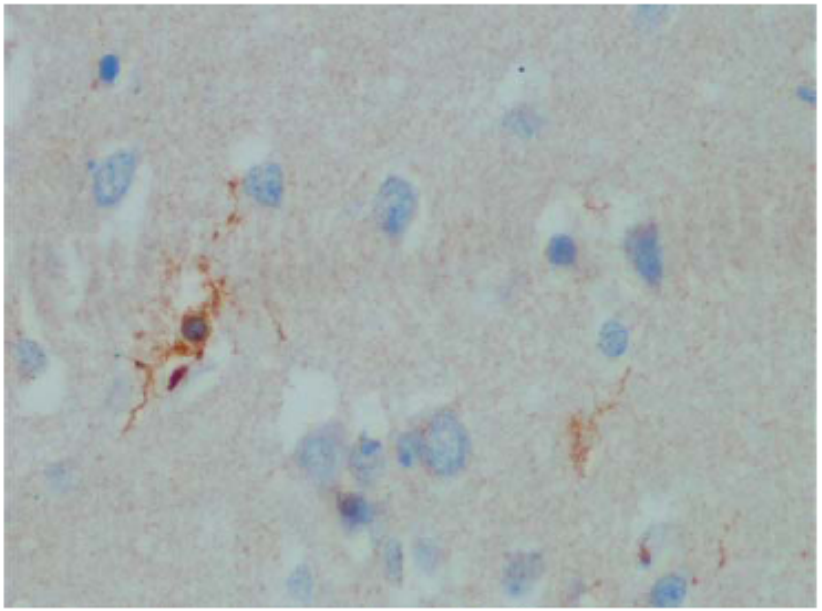


Fig. 2. Alzheimer's disease. Positive reaction to HLA DR on the surface of activated microglial cells, x400

Wojtera et al.,Folia Neuropathol, 43, 2005

Immune response in AD brain

- Inhibition of complement C3 activation in hAPP mice led to microglia deactivation, marked increase of beta-amyloid accumulation and neuronal degeneration[1]
- Microglia – activated by sensitized T cells as well
- Proinflammatory cytokines (IL-1beta, TNF-alpha, IL-6) – secreted by microglia and astrocytes - role in AD pathology – increased production of iNOS, neuronal stress and death[2]

1 – Wyss-Coray et al., Proc Natl Acad Sci USA, 99, 2002
2 – Schultzberg et al., Physiol Behav, 92, 2007

Neuroinflammatory hypothesis in AD

- Microglia accumulation at the amyloid plaques
- Microglia immune activation
- In affected brains – detection of proinflammatory cytokines, complement components, MHC II receptors, colocalized with microglia
- Aβ treatment of microglia in culture conditions triggers production of neurotoxins (proteolytic enzymes, cytokins, free radicals, TNFα, etc.)

J. Cell. Mol. Med. Vol 11, No 4, 2007 pp. 810-825

Studies on brain volume, Alzheimer-related proteins and cytokines in mice with chronic overexpression of IL-1 receptor antagonist

M. Oprica [a, *], E. Hjorth [a], S. Spulber [a], B. O. Popescu [b], M. Ankarcrona [c], B. Winblad [a], M. Schultzberg [a]

- IL-1 – one of the most important proinflammatory cytokines – both in physiology and pathology (response to infection, overexpressed both in stroke and AD, brain development, modulation of sleep, learning and memory, etc.)
- IL-1 system: IL-1 alpha, IL1-beta, IL1-ra – IL1-R1
- IL-1-ra expression induced by experimental stroke and KA (TLE model)

Oprica et al, 2007

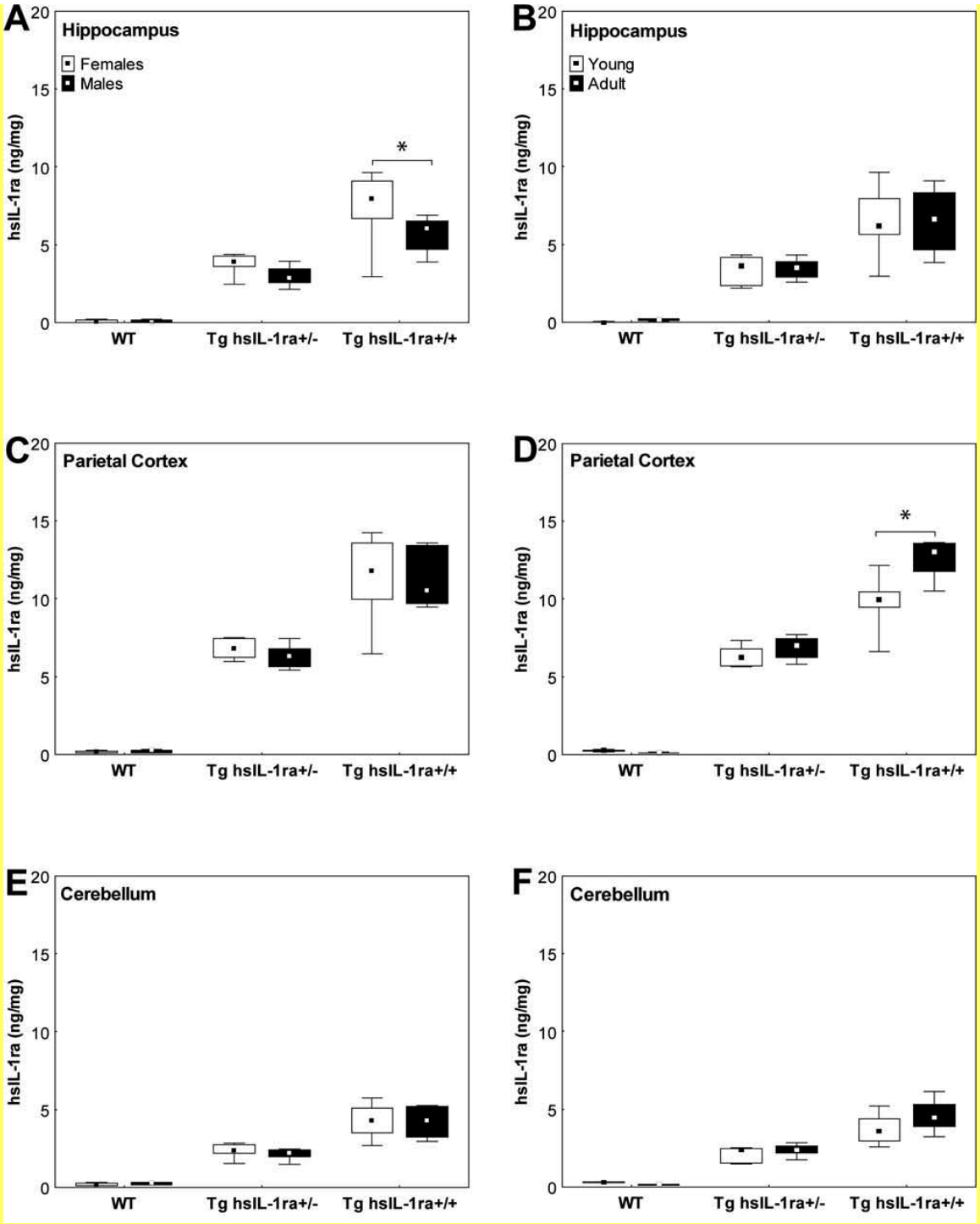
- IL-1, IL-6 have been demonstrated to significantly influence the synthesis and metabolism of APP
- IL-1 beta and TNFalpha increase gamma- and beta-secretases activity
- The objective of this study was to evaluate consequences of the **central blockade of IL-1** transmission in a previously developed transgenic mouse strain with *brain-directed* overexpression of **human soluble IL -1 receptor antagonist** (Tg hsIL-1ra)

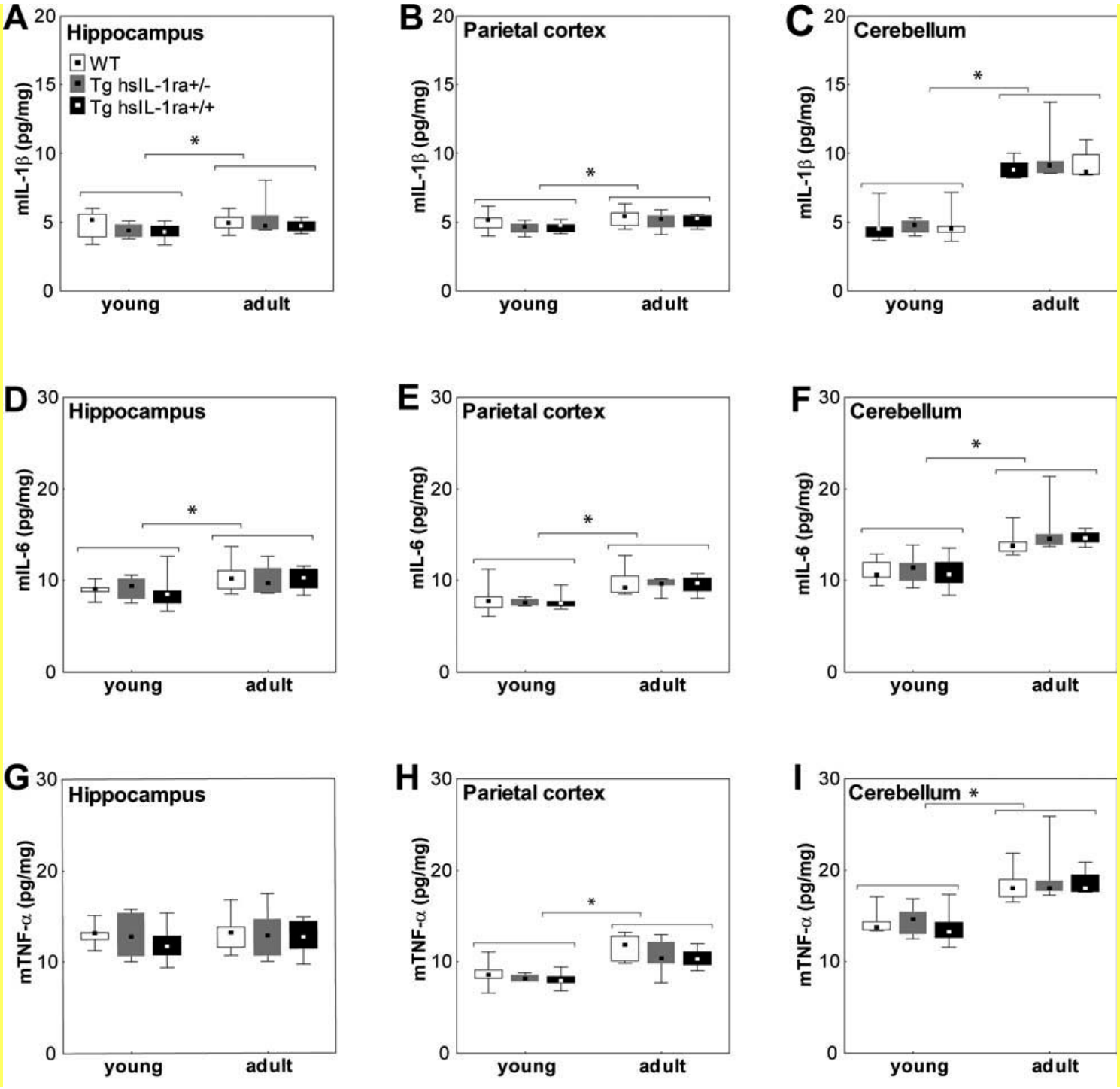
Materials and methods

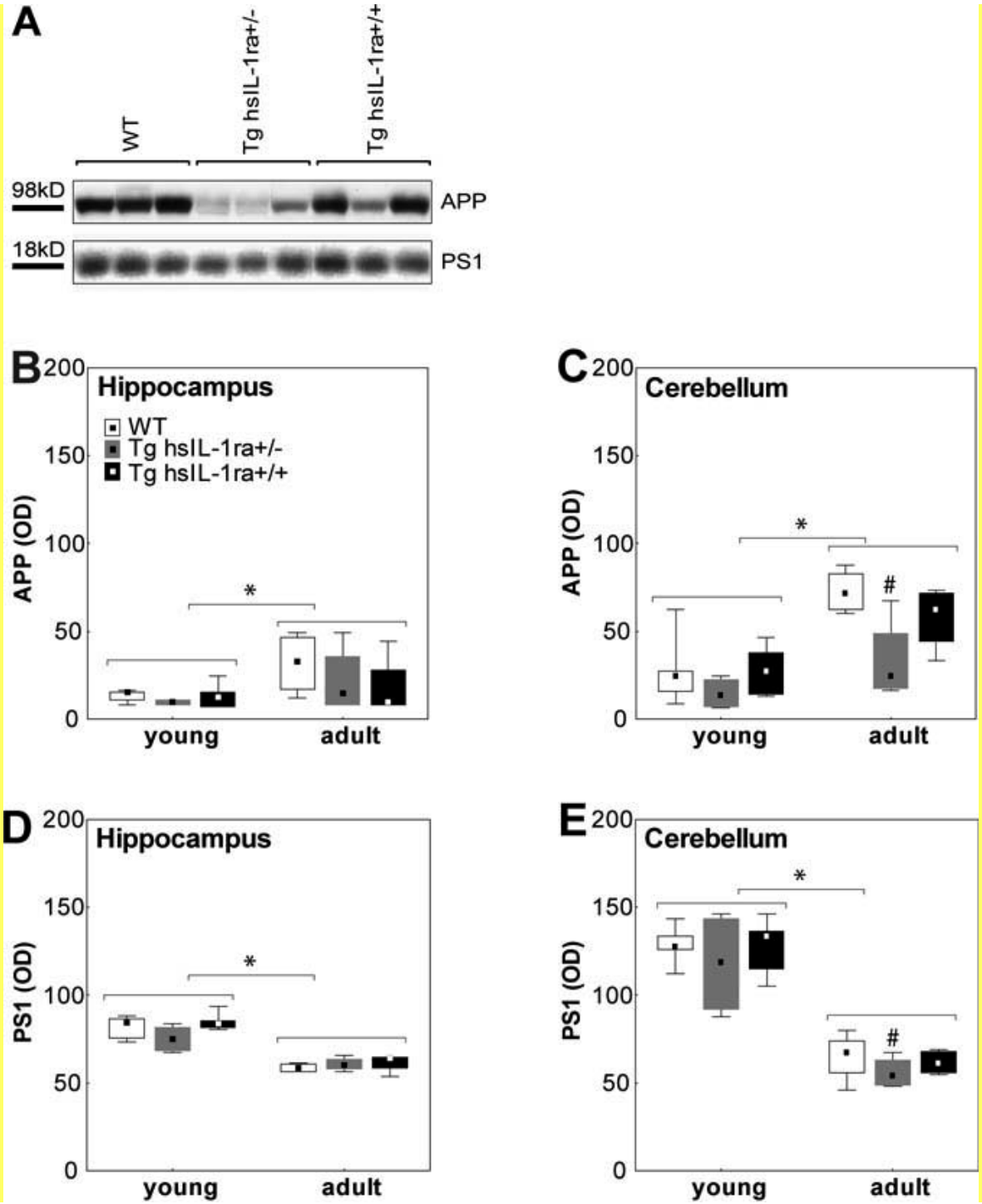
- Tg hsIL-1ra was developed previously using C57B6/CBA (Charles River, Germany) as the background strain

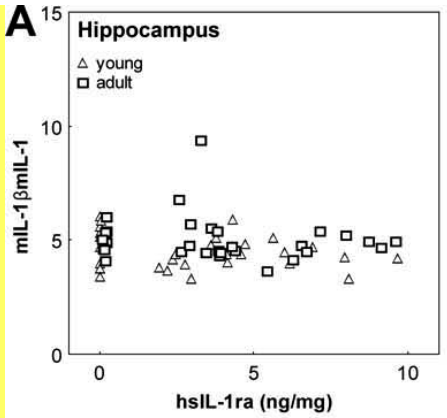
- Homozygotic (Tg hsIL-1ra+/+), heterozygotic (Tg hsIL-1ra+/–) and WT littermates of 30–40 days and 13–14 months were bred in the animal facility at Karolinska University Hospital Huddinge, and used for the studies on cytokine production.

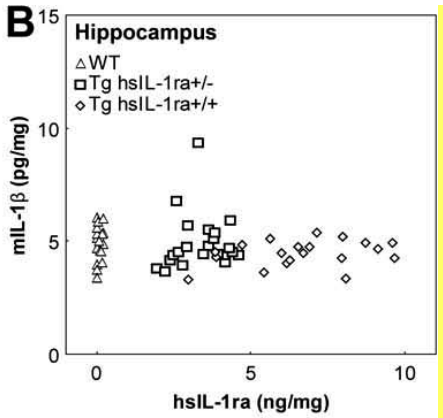
- Levels of the transgene product (hsIL-1ra), and of murine (m) IL-1β, mIL-6 and mTNF-α, were analysed by ELISA Duoset Development kits (R&D systems, Abingdon, UK) in brain samples

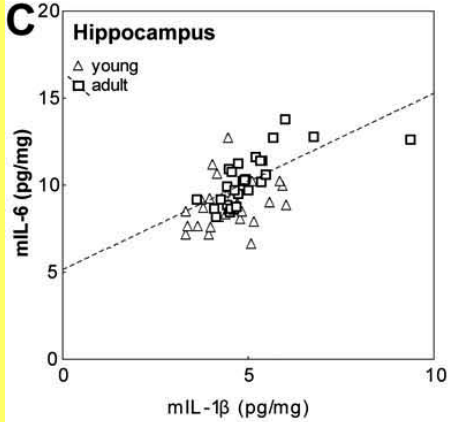

A
Hippocampus
Females
Males
hsIL-1ra (ng/mg)
0
5
10
15
20
*
WT
Tg hsIL-1ra+/-
Tg hsIL-1ra+/+
B
Hippocampus
Young
Adult
hsIL-1ra (ng/mg)
WT
Tg hsIL-1ra+/-
Tg hsIL-1ra+/+
C
Parietal Cortex
hsIL-1ra (ng/mg)
WT
Tg hsIL-1ra+/-
Tg hsIL-1ra+/+
D
Parietal Cortex
*
hsIL-1ra (ng/mg)
WT
Tg hsIL-1ra+/-
Tg hsIL-1ra+/+
E
Cerebellum
hsIL-1ra (ng/mg)
WT
Tg hsIL-1ra+/-
Tg hsIL-1ra+/+
F
Cerebellum
hsIL-1ra (ng/mg)
WT
Tg hsIL-1ra+/-
Tg hsIL-1ra+/+

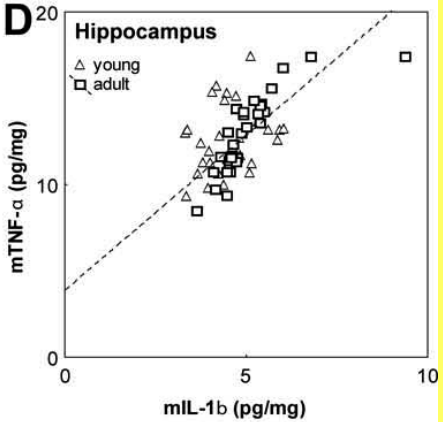

A
Hippocampus
WT
Tg hsIL-1ra+/-
Tg hsIL-1ra+/+
mIL-1β (pg/mg)
young
adult
B
Parietal cortex
C
Cerebellum
D
Hippocampus
mIL-6 (pg/mg)
E
Parietal cortex
F
Cerebellum
G
Hippocampus
mTNF-α (pg/mg)
H
Parietal cortex
I
Cerebellum

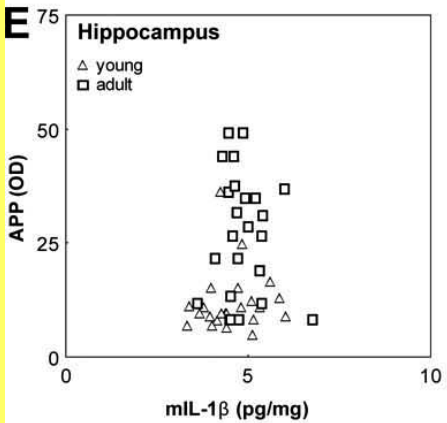

A
WT
Tg hsIL-1ra+/-
Tg hsIL-1ra+/+
98kD
APP
18kD
PS1
B
Hippocampus
WT
Tg hsIL-1ra+/-
Tg hsIL-1ra+/+
APP (OD)
200
150
100
50
0
young
adult
*
C
Cerebellum
APP (OD)
#
D
Hippocampus
PS1 (OD)
E
Cerebellum
PS1 (OD)

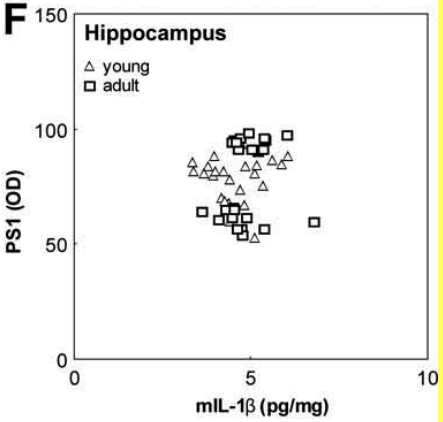

A
Hippocampus
young
adult
mIL-1βmIL-1
hsIL-1ra (ng/mg)
0
5
10
15


B
Hippocampus
WT
Tg hsIL-1ra+/-
Tg hsIL-1ra+/+
mIL-1β (pg/mg)
hsIL-1ra (ng/mg)
0
5
10
15

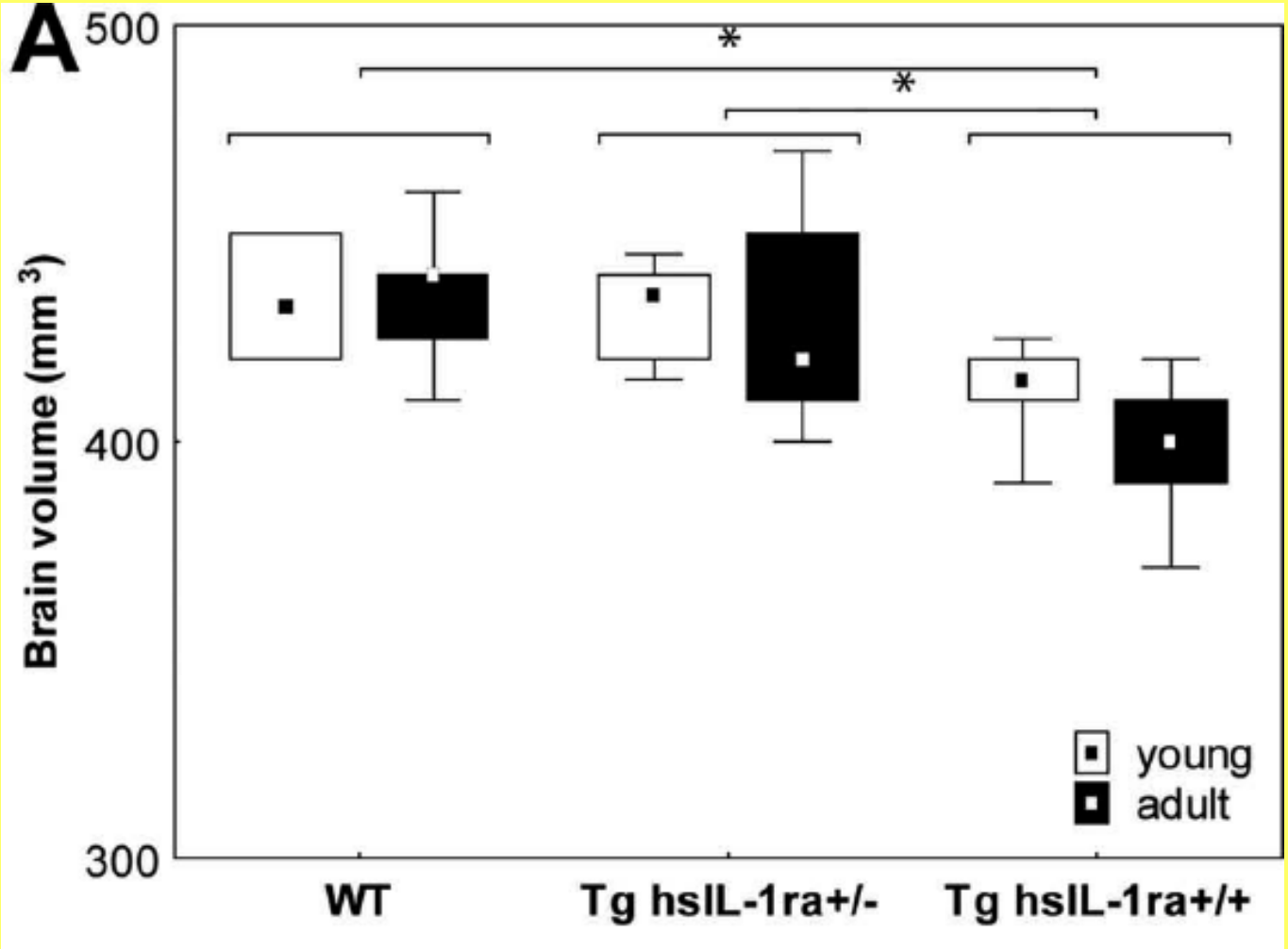

C
Hippocampus
young
adult
mIL-6 (pg/mg)
mIL-1β (pg/mg)
0
5
10
15
20


D
Hippocampus
young
adult
mTNF-α (pg/mg)
mIL-1b (pg/mg)
0
5
10
20

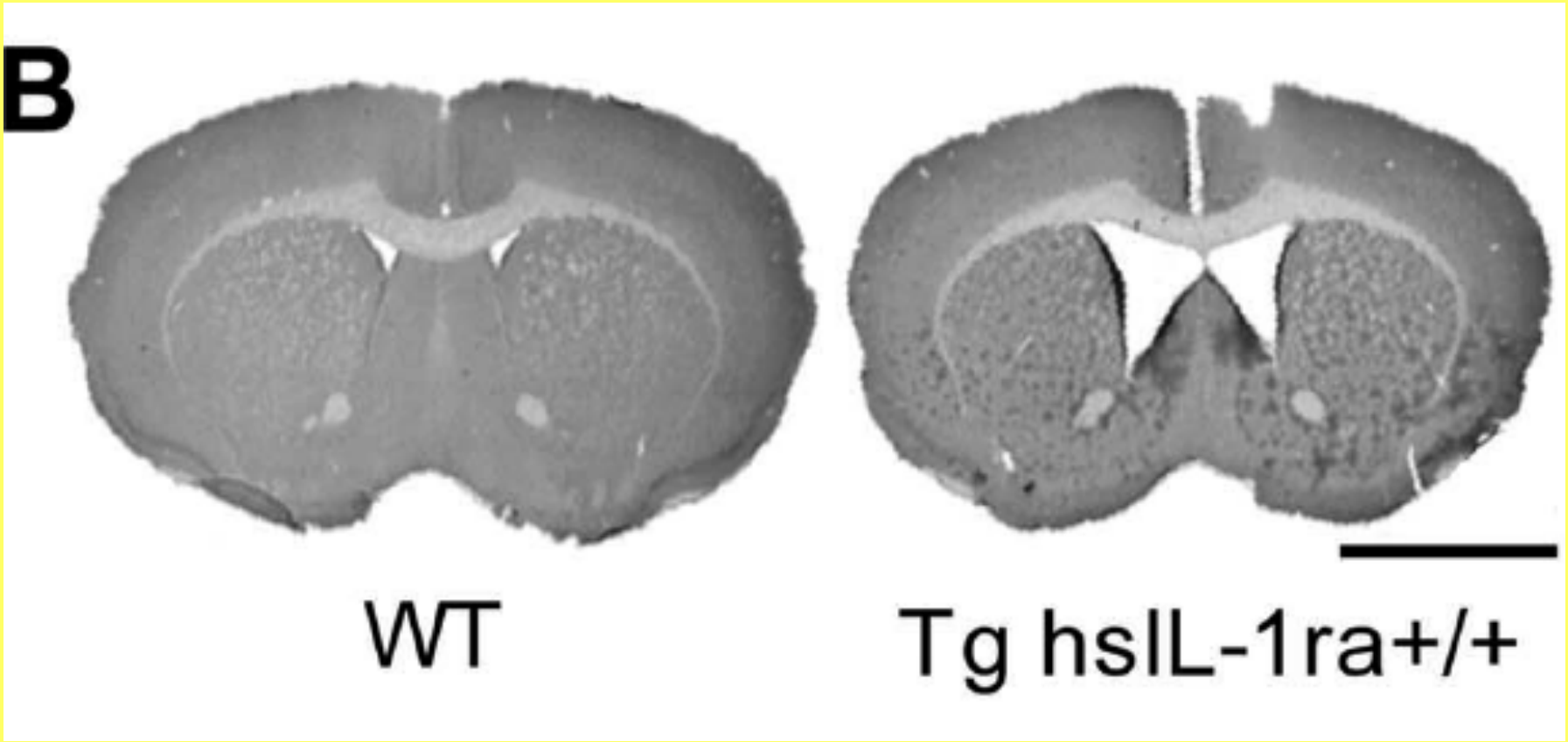

E
Hippocampus
young
adult
APP (OD)
mIL-1β (pg/mg)
0
5
10
25
50
75


F
Hippocampus
young
adult
PS1 (OD)
mIL-1β (pg/mg)
0
5
10
50
100
150

Oprica et al, 2007

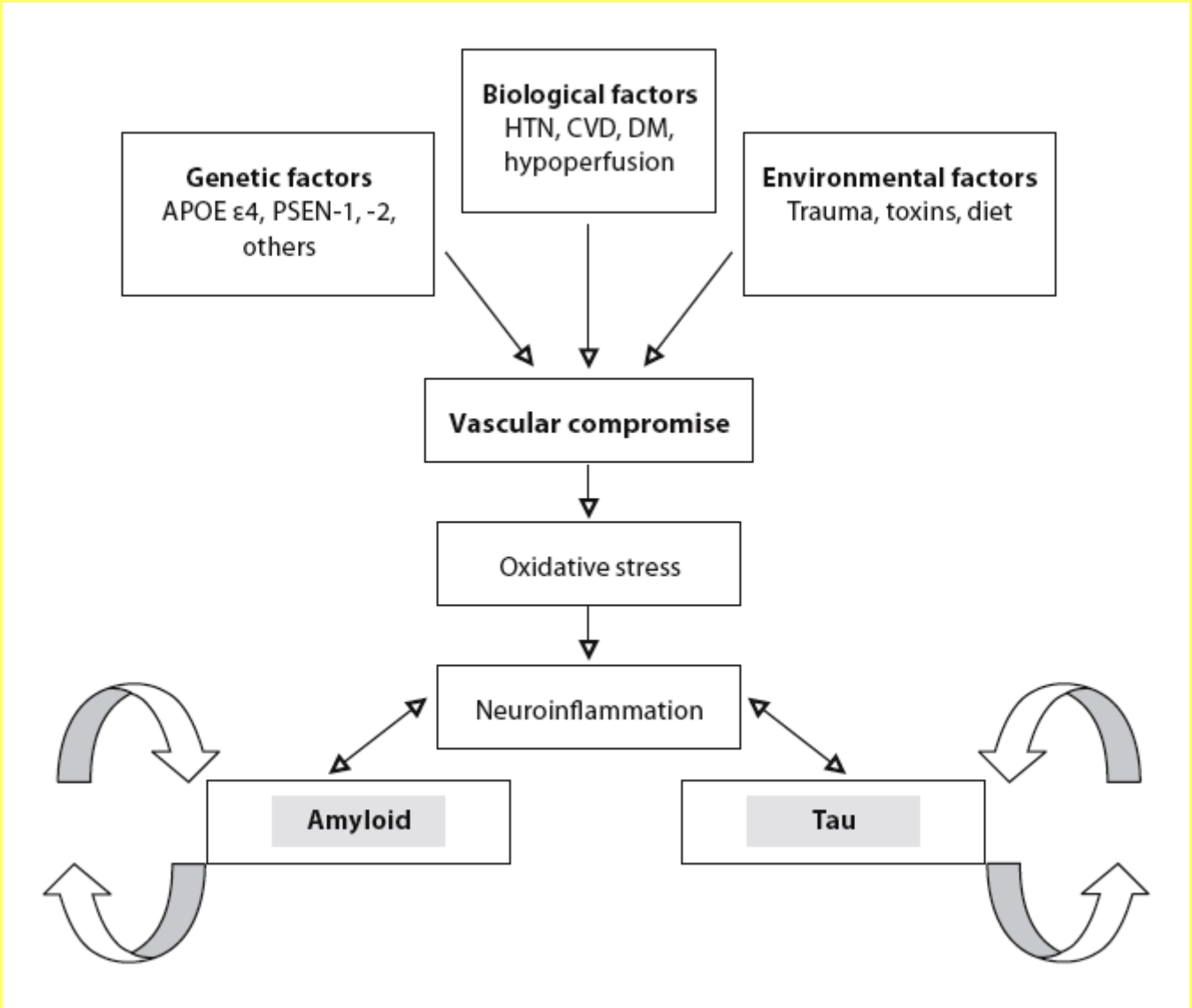


Oprica et al, 2007

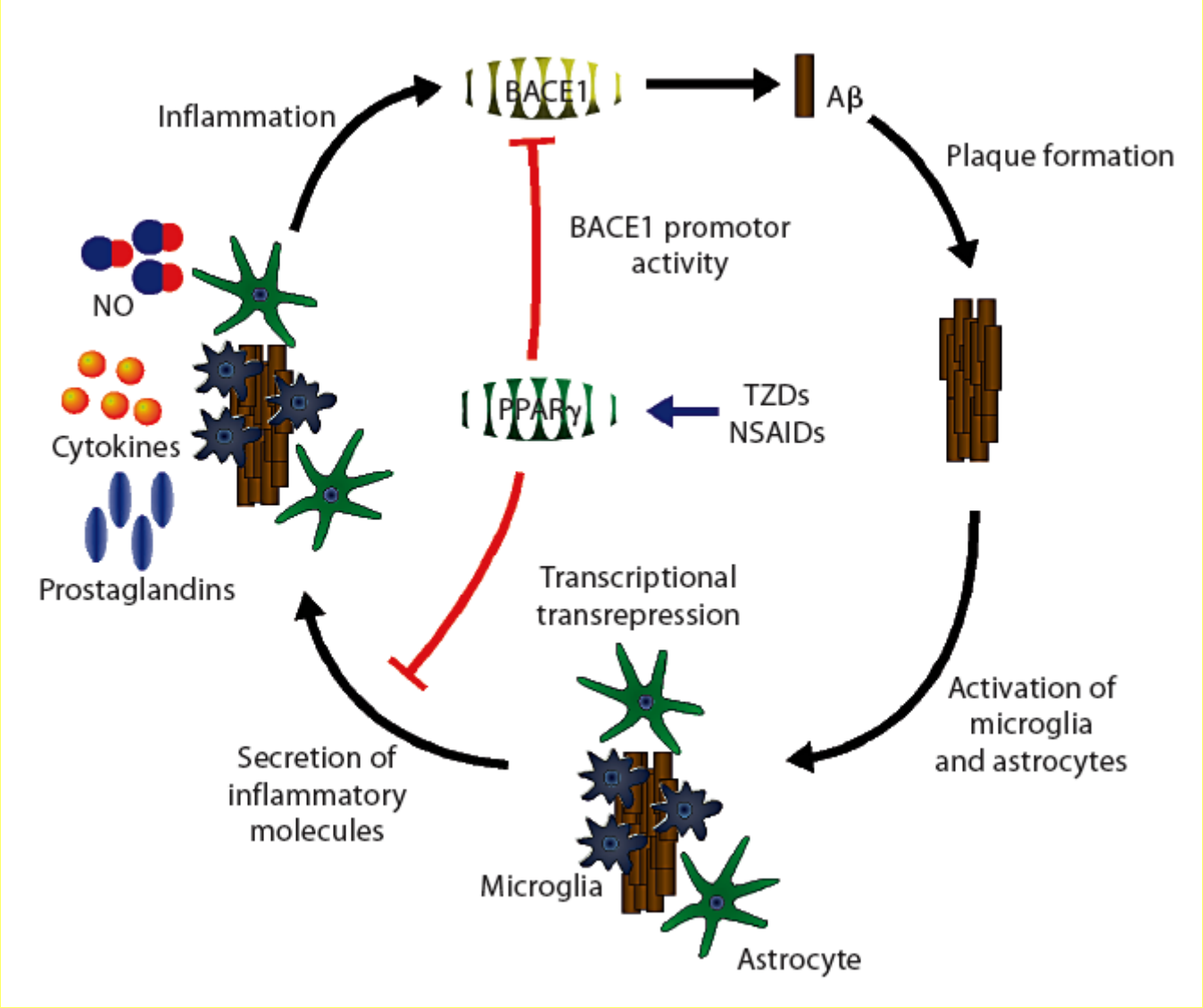


Conclusions

- A marked reduction in brain volume was observed in transgenic mice as determined by volumetry.
- Western blot analysis showed higher levels of APP, but lower levels of PS1, in adult animals than in young ones.
- Blocking IL-1 signalling does not trigger compensatory changes in pro-inflammatory cytokines levels (IL-1β, IL-6 and TNF-α).
- Age is correlated with higher cytokines levels (mechanism for ageing risk for dementia?)



McNaull et al, Gerontology, 56, 2010



TSDs= Thiazolidinediones, PPR=Peroxisome Proliferator-Activated Receptors

McNaull et al, Gerontology, 56, 2010

AD therapy targets based on neuroinflammatory theory

- LOAD – multifactorial disease
- Many events lead to neuroinflammation, and this is one major AD pathogenic operator
- Actual treatment – week effects, ACEI, memantine
- NSAIDs, oestrogen, statins and vitamin E (antiinflammatory effects) – clinical trials negative
- Probably multifactorial interventions needed
- Dietary restriction – reduces the system-wide inflammatory processes
- Etanercept (antagonist of TNF alpha) - promising (improves MMSE, verbal fluency, apraxia over 6 months)
- Target RAGE (blocking)/LRP (stimulating) receptors?

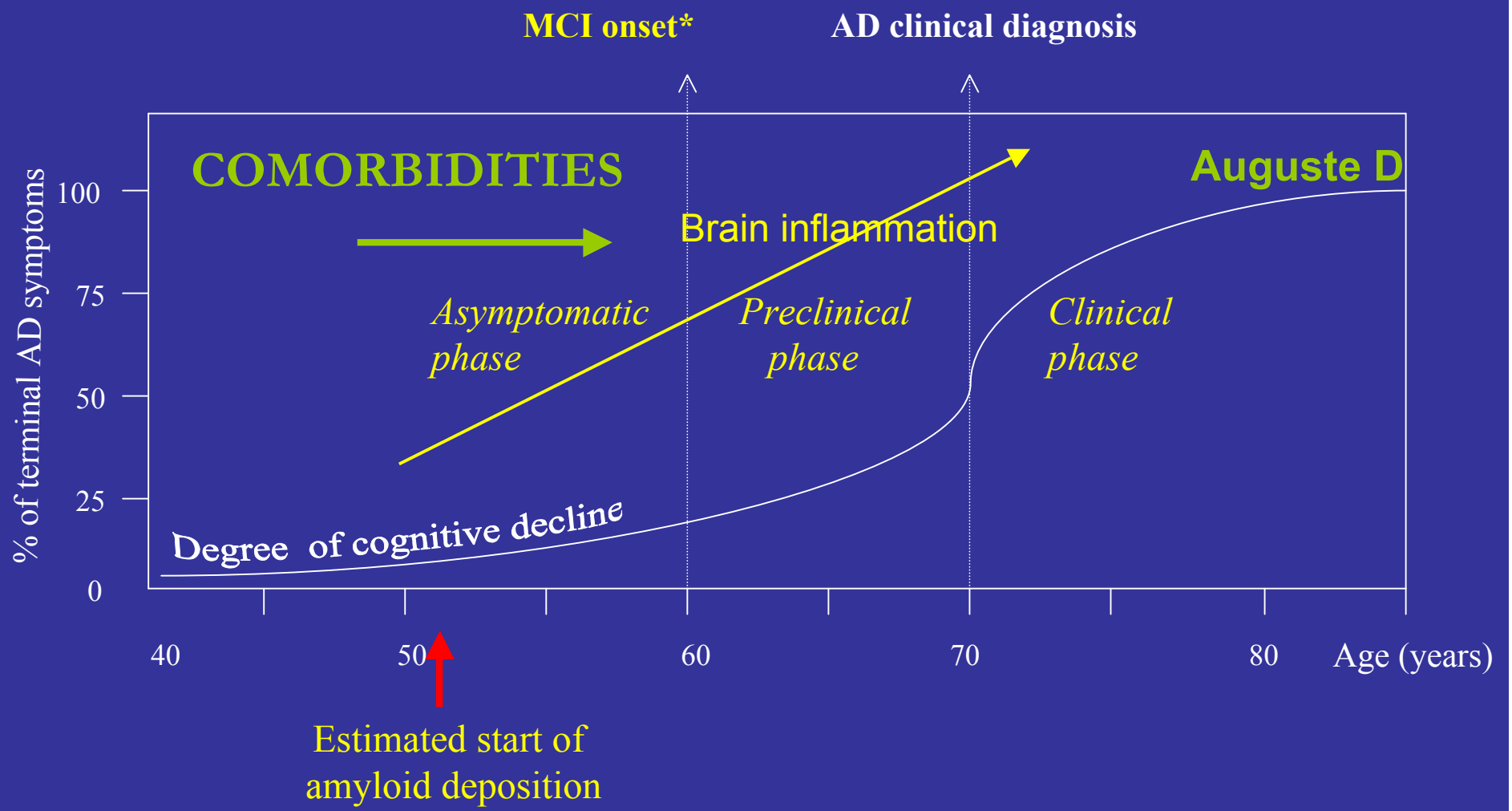
Vaccination for AD?

- Beta-amyloid or non-beta-amyloid peptide vaccine active/passive (1-42 – 1-15)
- DNA vaccine (plasmids to trigger expression of different beta-amyloid species)
- Recombinant vegetable (for oral vaccine)
- Recombinant viral vectors

- Maybe to be tried in MCI or aged only?

Takeshi Tabira, Tohoku J Exp Med, 220, 2010

Hypothetical natural evolution of sporadic AD – it is not a straight line



*MCI-mild cognitive impairment

Modified after PJ Visser, 2000