OECD Global Coalition on Aging
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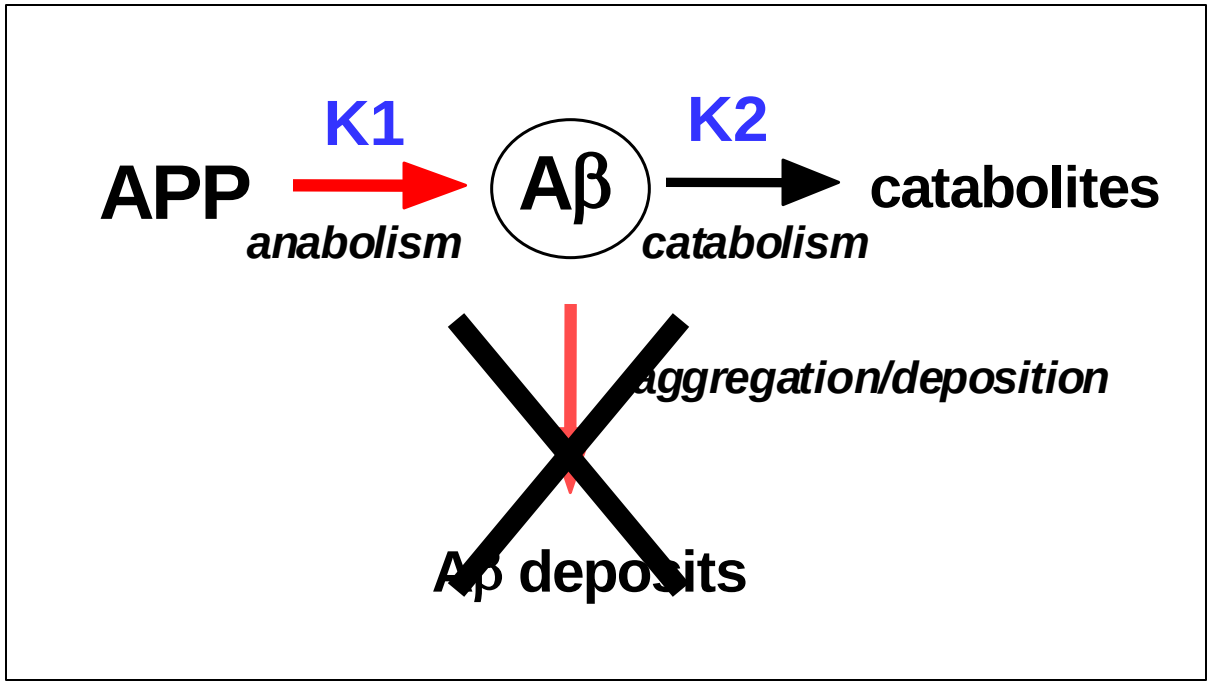
Gene therapy and 2nd generation mouse models of Alzheimer's disease

Takaomi C. Saido
Laboratory for Proteolytic Neuroscience
RIKEN Brain Science Institute
JAPAN

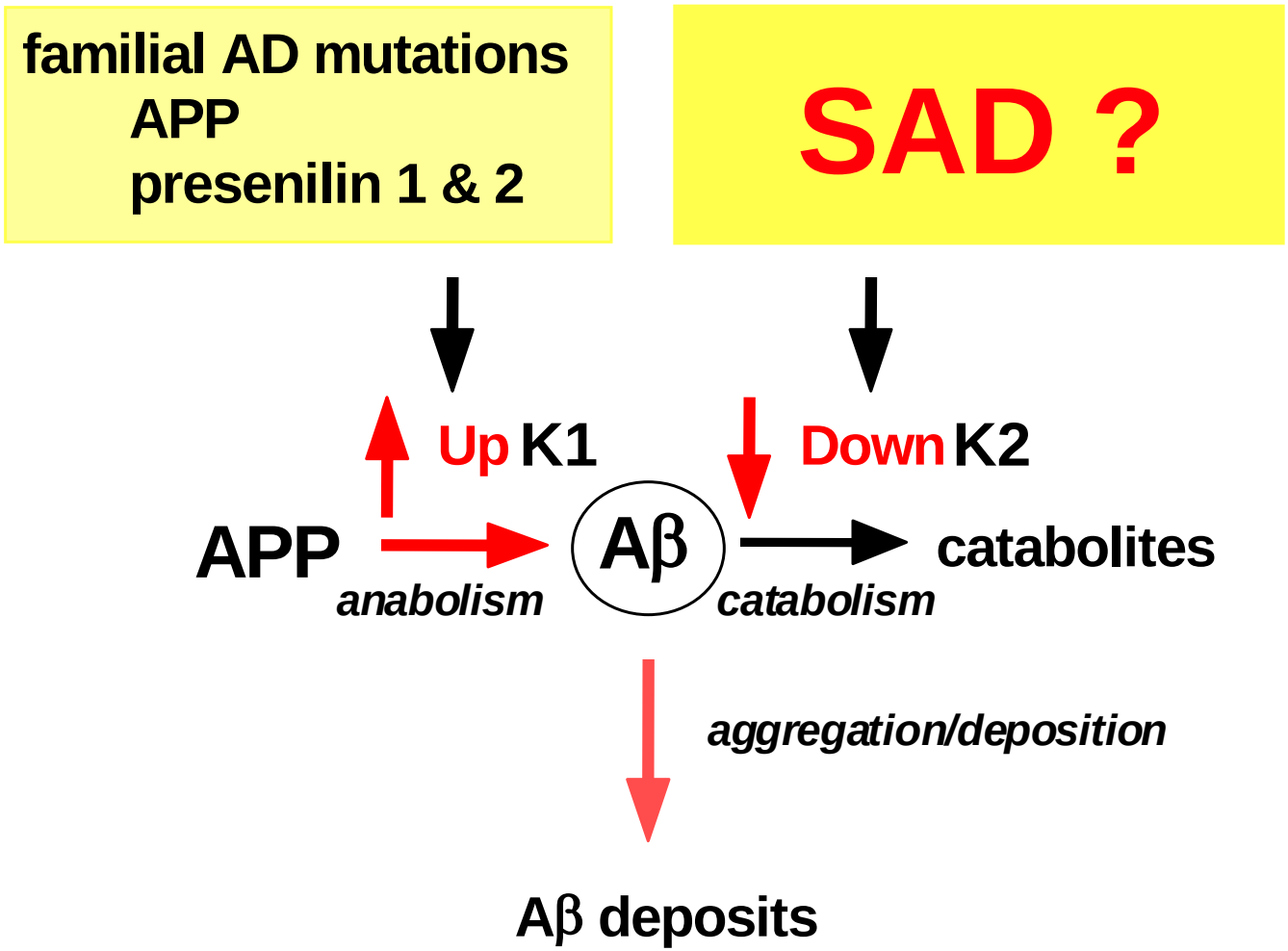
Metabolism of Aβ under steady-state conditions



Under steady-state conditions:

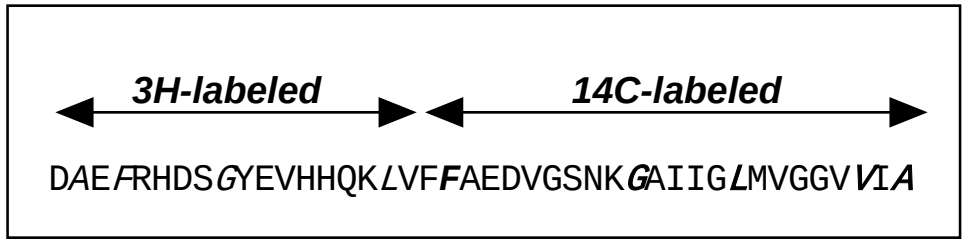
[Aβ] = K1/K2 x [APP]

What is the cause for Aβ deposition in SAD?

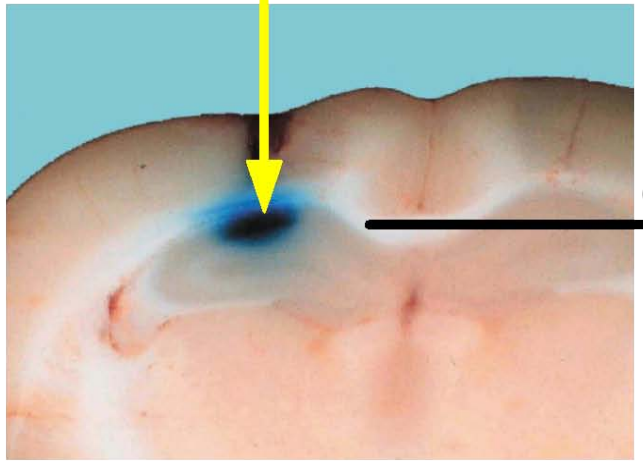


Analysis of *in vivo* Aβ1-42 catabolism

Radiolabeled Aβ1-42



stereotaxic injection*



extraction

Analysis by radio-HPLC

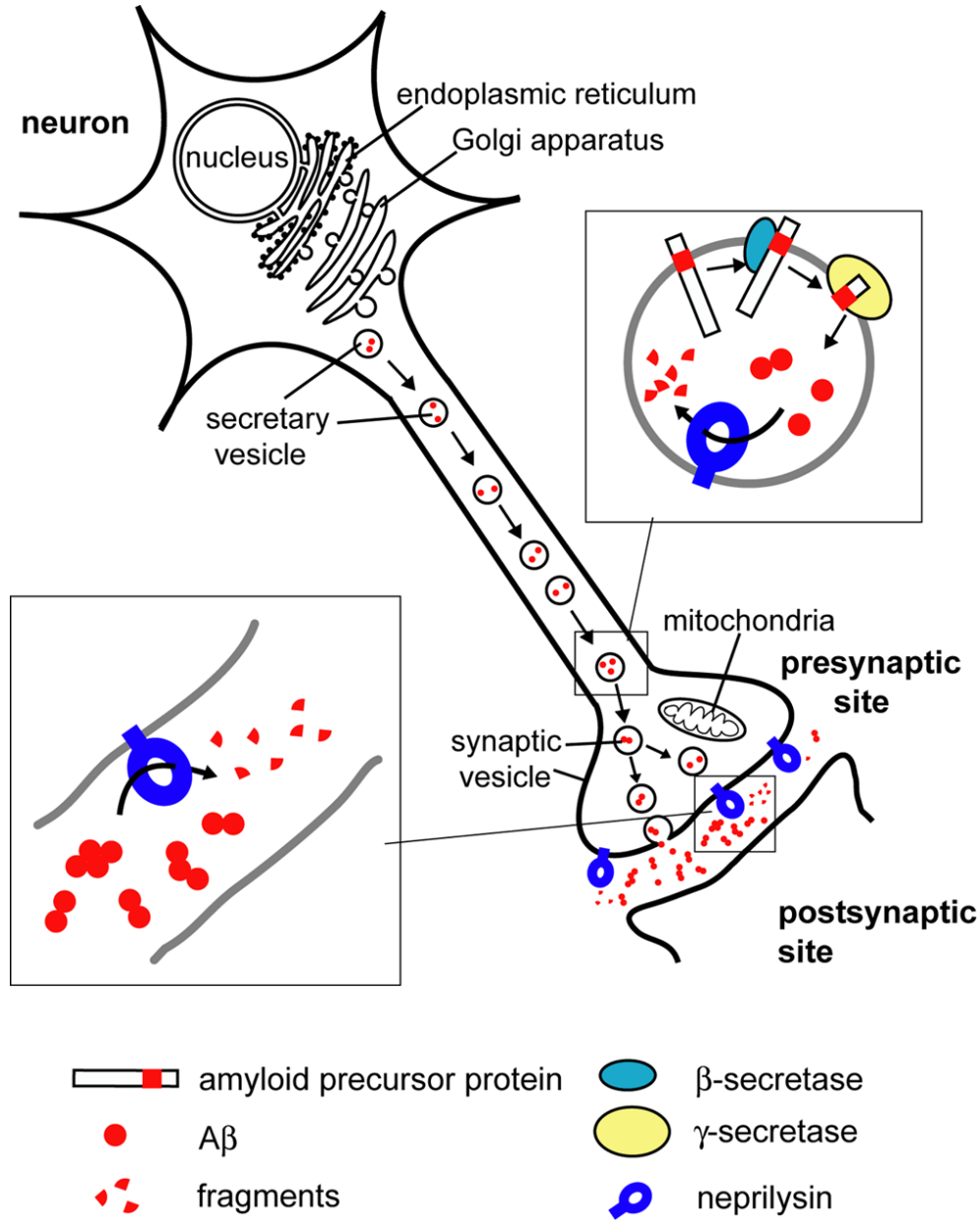
HPLC

scintillation analyzer

Nat Med (2000)

Neprilysin degrades synaptotoxic Aβ oligomers.

Neprilysin is the only peptidase that can degrade Aβ monomer & oligomers at synapses.



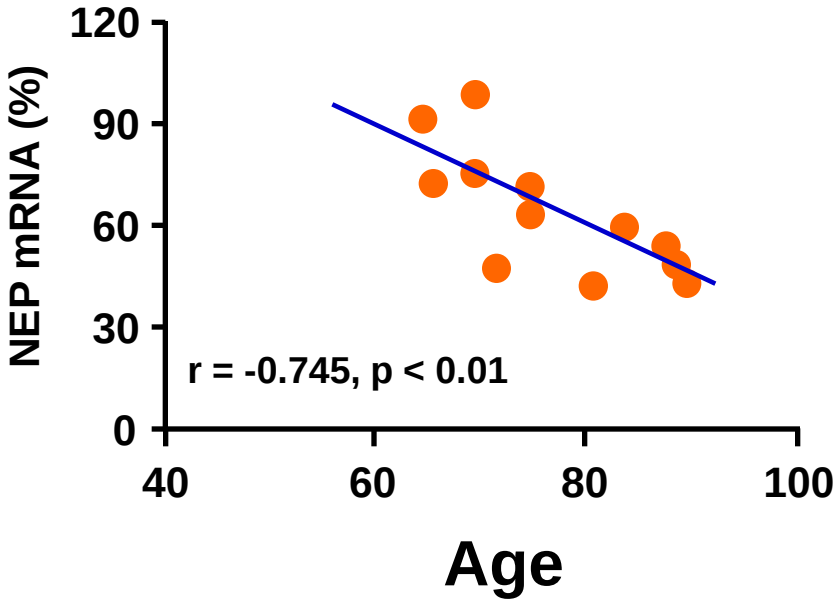
Neprilysin activity can be utilized for prevention and treatment of Alzheimer's disease.

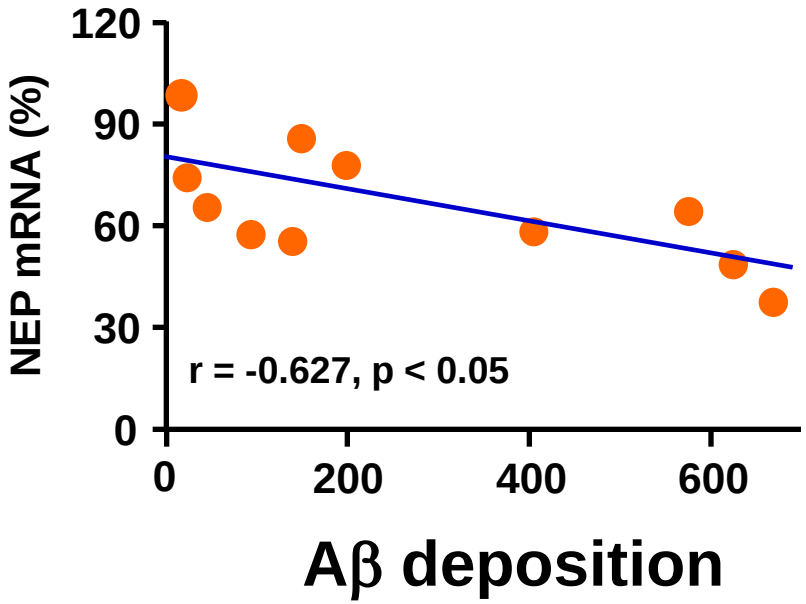
Nat Med (2000), Science (2001), Lancet (2003), Nat Med (2005), JBC (2006), JBC (2012).

Decline of neprilysin expression with aging

Hellström-Lindahl et al. Neurobiol. Aging 29, 210-221 (2008)

Temporal cortex





SCIENTIFIC REPORTS

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SUBJECT AREAS:
EXPERIMENTAL MODELS OF DISEASE
ALZHEIMER'S DISEASE
GENETIC VECTORS
PROTEASES

Global brain delivery of neprilysin gene by intravascular administration of AAV vector in mice

Nobuhisa Iwata[1,2], Misaki Sekiguchi[1], Yoshino Hattori[2], Akane Takahashi[2], Masashi Asai[2], Bin Ji[3], Makoto Higuchi[3], Matthias Staufenbiel[4], Shin-ichi Muramatsu[5] & Takaomi C. Saido[1]

1. **Selective expression of neprilysin in brain**
2. **Reduction of Aβ pathology**
3. **Recovery of cognitive dysfunction**

Discussion

1. Aging-dependent downregulation of neprilysin activity is likely to contribute to etiology of SAD.

2. Gene therapy using neprilysisn will be one of the promising options in prevention and treatment of AD.