Gene therapy and 2nd generation mouse models of Alzheimer’s disease

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Metabolism of Aβ under steady-state conditions

Under steady-state conditions:

\[ [A\beta] = \frac{K_1}{K_2} \times [APP] \]
What is the cause for Aβ deposition in SAD?

familial AD mutations
APP
presenilin 1 & 2

SAD?

APP
anabolism

Aβ

Aβ deposits

catabolism

catabolites

aggregation/deposition

K1

K2

Up

Down
Analysis of \textit{in vivo} A\textsubscript{β}1-42 catabolism

Radiolabeled A\textsubscript{β}1-42

\begin{align*}
&\text{3H-labeled} & \text{14C-labeled} \\
&\text{DAEFRHDSGYEVHQLVF} & \text{FAEDVGSNKGAIgLMMGGLVIA}
\end{align*}

* stereotaxic injection

Analysis by radio-HPLC

HPLC

scintillation analyzer

Neprilysin degrades synaptotoxic Aβ oligomers.

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

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

Decline of neprilysin expression with aging


Temporal cortex

Decline of neprilysin expression with aging


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

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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 neprilysin will be one of the promising options in prevention and treatment of AD.