A promising phospholipase A2-targeted peptide slowing amyloid beta pathology in an Alzheimer’s disease mouse model

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INTRODUCTION

Alzheimer disease (AD)

- Most common dementia worldwide with 2 main features: extracellular senile plaques of amyloid β (Aβ) & intracellular neurofibrillary tangles of tau protein
- Since 1993, no new drug was approved by FDA (> 95% failed during clinical trials) [1]
- Actual therapies are only symptomatic & do not slow the progression of the disease

In vivo molecular imaging: APP/PS1 mice (Jackson Laboratory, Maine, USA) were injected with 200µmol Fe/Ag b.w. of USP51-PH2 [4]. Then, images were acquired at the level of the head with T₂-weighted RARE imaging protocol (TR/TE = 3000/60 ms; RARE factor = 4, NEX = 6, matrix = 512x512, FOV = 2.5 cm, slice thickness 1mm, 20 axial slices, spatial resolution 48µm, TA = 38m24sec).

Barnes maze: study of the spatial memory of non treated healthy mice and APP/PS1 mice during the period of treatment with PLP25-LRP1 or NSP (1.5 month). All performances were recorded and analyzed manually.

Immunohistochemistry: detection of AP, APP, PLA₂, NMDAR and p-tau

RESULTS

After 1.5 months of treatment, the injection of PLA₂-LRP1 to APP/PS1 mice reduced the number and size of AP in contrast to NSP injection, whereas older and non-treated mice show AP progression. (B) AP were counted manually in the whole brain and the hippocampus of mice treated with PLA₂-LRP1 or NSP and in older APP/PS1.

Detection of amyloid precursors protein (APP) by IHC. The labeling obtained for PLP25-LRP1 treated mouse is intermediate between the 3-months-diseased mice (more amyloids) and healthy mice (nearly remembrance) with a closer approach to healthy mice.

CONCLUSION

PLP25-LRP2 incubation with cells showed to:
- Prevent the production of Aβ by Glu-stimulated cells;
- Prevent the Glu- and Aβ-induced PLA₂ translocation to cell membranes
- Prevent COX2 and ALOX translocation after Glu stimulation

PLP25-LRP2 injection to APP/PS1 mice allows to:
- Improve their cognitive abilities (Barnes maze results)
- Reduce the amount of amyloid plaques unlike NSP injection
- Increase the expression of NMDAR in healthy mice.


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Development of a therapeutic strategy by targeting a key actor in the phospholipase (PLA₂) signalling involved in AD using a peptide identified by phage display (PLP25) and rendered able to cross the BBB by coupling to a vector peptide (LRP2) targeting the LDLR.