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

AD management

- Only symptomatic treatments allowing a better quality of life for patients
- Various phospholipase isoforms involved in memory impairment and neurodegeneration in AD
- PLPα signaling pathway involved in AD [2] → PLPα inhibition has shown neuron protection against apoptosis induced by Aβ [3]

Development of an original phospholipase A2-targeted peptide able to reduce amyloid pathology in a mouse model of Alzheimer’s disease

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INTRODUCTION

Alzheimer disease (AD) is a progressive neurodegenerative disorder of the nervous system characterized by the deposition of amyloid β (Aβ) peptides in the extracellular space and neurofibrillary tangles of hyperphosphorylated tau protein in the cytoplasm of neuronal cell bodies. These deficits lead to cognitive impairment, memory loss, and ultimately, dementia. Despite decades of research, the development of effective treatments for AD remains challenging. Current therapies are aimed at symptom management rather than disease modification. This work focuses on the development of a therapeutic strategy targeting a key player in the phospholipase A2 (PLA2) signaling pathway involved in AD using a peptide identified by phage display (PLPα) and rendered able to cross the BBB by coupling to a vector peptide (LRPα) targeting the LDLR.

RESULTS

In vitro

- Figure 2: The glucoseamine shows a cytotoxic effect on PLP, paracrine control, compared to the negative control (non-pretreated and non-activated cell), as demonstrated by cell viability assay. The reduced PLP viability indicates the cytotoxic effect and is served as a negative control in the in vitro studies.

- Figure 3: Immunofluorescence analysis of mouse brain sections revealed an increase in the expression of Aβ and Aβ deposition in AD mice compared to healthy controls. The staining was performed using specific antibodies targeting Aβ, which labels the plaques.

In vivo

- Figure 4: The inhibition of PLPα in the brain of AD mice treated with AD drug showed a decrease in Aβ plaque formation and accumulation compared to the control group. This supports the reduction in Aβ levels in the AD model treated with PLPα.

- Figure 5: Immunohistochemistry analysis of brain sections from AD mice treated with PLPα revealed a significant reduction in Aβ plaques formation, indicating a possible therapeutic effect of the peptide in vivo.

CONCLUSION

The in vitro and in vivo studies demonstrated the potential of PLPα in reducing Aβ plaque formation and neuronal cell death in AD models. Further studies are required to fully understand the mechanism of action and to develop a safe and effective therapeutic strategy for AD treatment.

METHODS

- Inhibitory potential of PLPα: Pre-incubation of differentiated N17/21 cells during 30 minutes with 200µM PLPα before induction with glutamate (50µM) → Aβ dose (AA EUSA a 6, Cuabisi, USA)
- Immunofluorescence: subcellular localization of PLPα and p-PLPα in cell lysates, characterization of the subcellular localization and kinetics
- In vivo molecular imaging: APP/PS1 mice (Jackson Laboratory, Maine, USA) were injected with 200µg bFGF and [125I]-hSAP (4). Then, images were acquired at the level of the head with T2-weighted BARE imaging protocol (TR/TE = 4000/50 ms, BARE factor = 4, NEX = 4, matrix = 256x256, FOV = 5.2 cm, slice thickness 3mm, 20 axial slices, spatial resolution = 4mm, TA = 4min24sec).
- Barnes maze: study of the spatial memory of non treated healthy mice and APP/PS1 mice during the period of treatment with PLPα, LRPα, or KSP (1.5 months). All performances were recorded and analyzed manually.
- Immunohistochemistry: detection of Aβ, APP, PLPα, NFT, and p-tau

REFERENCES