



HAL
open science

Effect of Alzheimer's disease-related β -amyloid peptide conformations in transgenic mouse models of β -amyloidosis

Marina Célestine, Muriel Jacquier-sarlin, Eve Borel, Anne-sophie Herard,
Alain Buisson, Marc Dhenain

► To cite this version:

Marina Célestine, Muriel Jacquier-sarlin, Eve Borel, Anne-sophie Herard, Alain Buisson, et al.. Effect of Alzheimer's disease-related β -amyloid peptide conformations in transgenic mouse models of β -amyloidosis. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association*, 2020, 16 (S2), 10.1002/alz.043415 . hal-03453388

HAL Id: hal-03453388

<https://hal.science/hal-03453388>

Submitted on 28 Nov 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Development of new models and analysis methods/seeding and spreading of proteinopathies

Effect of Alzheimer's disease-related β -amyloid peptide conformations in transgenic mouse models of β -amyloidosis

Marina Célestine¹ | Muriel Jacquier-Sarlin² | Eve Borel² | Anne-Sophie Herard³ | Alain Buisson² | Marc Dhenain⁴

¹ CEA, Fontenay-aux-Roses, France

² Université de Grenoble Alpes/Institut de Neurosciences de Grenoble (GIN), Grenoble, France

³ Paris-Saclay University, Fontenay-aux-Roses, France

⁴ Centre National de la Recherche Scientifique (CNRS), Fontenay-aux-Roses, France

Correspondence

Marina Célestine, CEA, Fontenay-aux-Roses, France.

Email: marina.celestine@cea.fr

Abstract

Background: Alzheimer's disease (AD) brain dysfunctions are not exclusively related to amyloid plaques occurrence, but are thought to start much earlier, presumably due to soluble pathological forms of β -amyloid peptide ($A\beta$). Indeed $A\beta$ oligomers induce synaptic dysfunctions that cause cognitive decline, exacerbate tau pathology[1] and influence neuronal networks[2]. Although mutation-induced phenotypes are identified in AD patients, the *in vivo* effects of different $A\beta$ variants are poorly understood. Here we characterized the effects of different $A\beta$ variants in a transgenic mouse model to provide deeper insight of transconformational processes and the subsequent alterations. Deciphering $A\beta$ profiles would help in developing new diagnostic and therapeutic approaches.

Method: We developed well-characterized amyloid variants: $A\beta$ 1-42, $A\beta$ bearing the icelandic mutation (A2T), $A\beta$ bearing the Osaka mutation (E22D[1]) and $A\beta$ bearing the mutation F19S/L34P. First, these variants were overexpressed in cortical neuron cultures. Then, two-month-old APP/PS1dE9 mice were inoculated with these variants in the dentate gyrus (n = 5/per group). We assessed $A\beta$ oligomerization profiles, cerebral amyloid load and synaptic health in neuron and mouse (4 months post-inoculation) models by biochemistry and histology.

Result: The different amyloid forms exhibit distinct aggregation profiles and synaptotoxicity *in vitro* (Figure 1). They did not have the same effect on mouse survival. Osaka- $A\beta$ induced the highest mortality. Then, we focused on the local reorganization of amyloid. Osaka- $A\beta$ led to increased 6-mer and 12-mer amyloid forms at inoculation site (Figure 2) but also at distance in the cortex. This suggests that $A\beta$ variants differently modulate $A\beta$ metabolism and aggregation. Amyloid plaque assessment showed

an Osaka- $A\beta$ -induced increase in amyloid load in the hippocampus (Figure 3) and its connected regions.

Conclusion: A single inoculation of different $A\beta$ variants in APP/PS1dE9 mice expressing wild-type $A\beta$ is sufficient to differentially modulate $A\beta$ metabolism, amyloid load and mouse mortality. This suggests that $A\beta$ variants differentially interact with the biochemical/biophysical cerebral environments to differentially induce toxic downstream events that are crucial for better AD physiopathology understanding. References: (1) Delacourte et al., *Experimental Gerontology*, 2002. (2) Bero et al., *Journal of Neuroscience*, 2012. (3) Tomiyama et al., *Ann Neurol*, 2008.

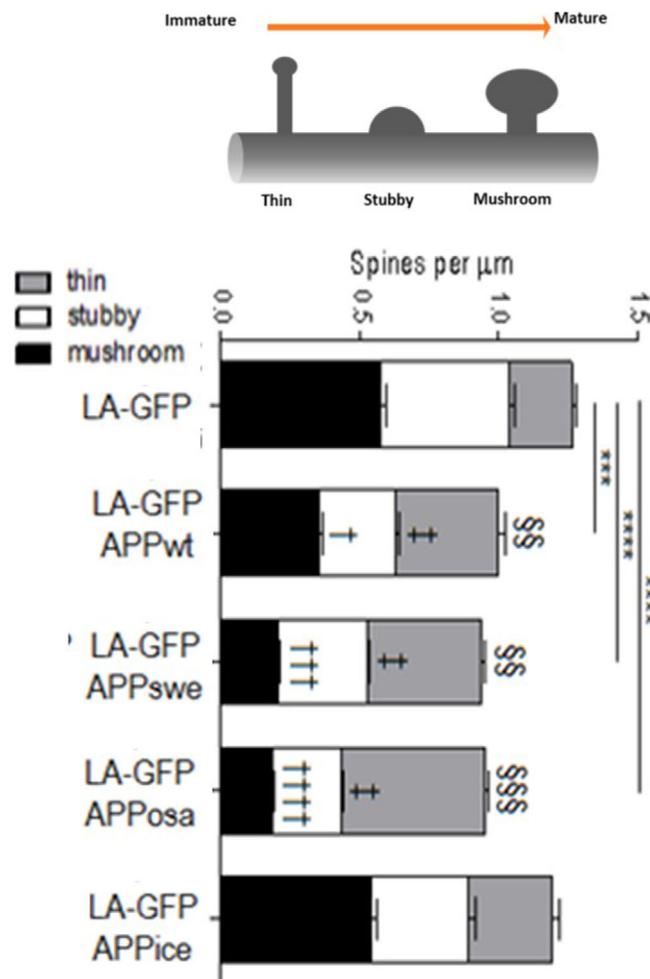


FIGURE 1

Hippocampus

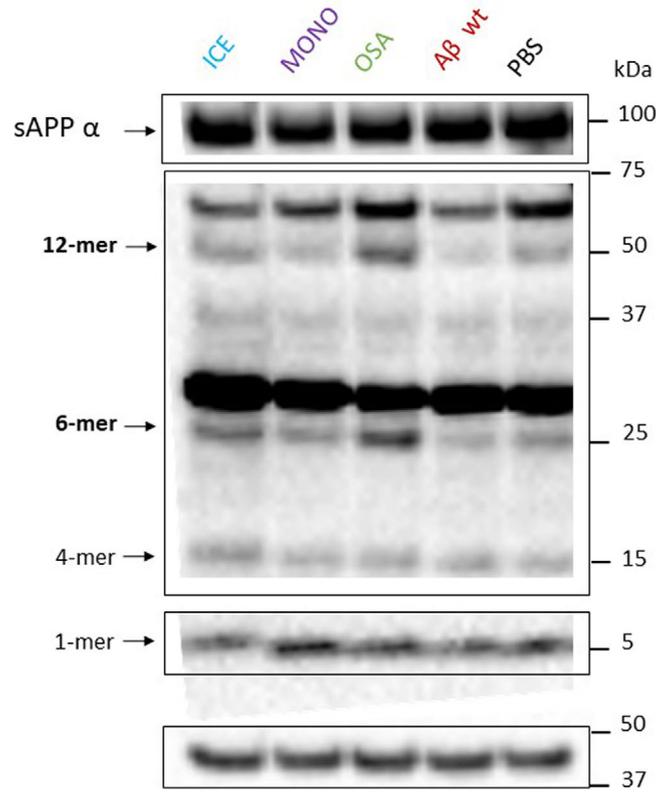


FIGURE 2

Hippocampus

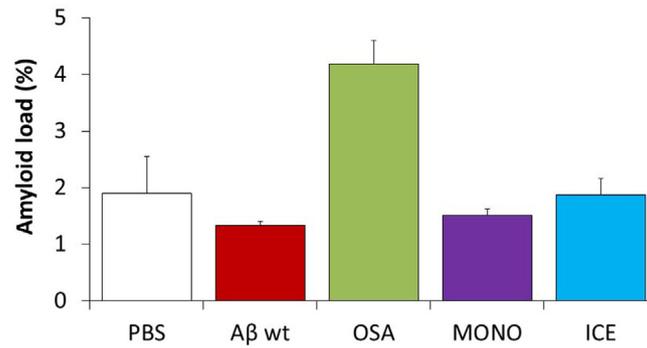


FIGURE 3