D-SERINE IS INVOLVED IN THE 
β-AMYLOID-RELATED PATHOPHYSIOLOGY IN 
ALZHEIMER’S DISEASE

E Ploux, L. Gorisse, I Radzishevsky, H Wolosker, T Freret, J-M Billard

To cite this version:
E Ploux, L. Gorisse, I Radzishevsky, H Wolosker, T Freret, et al.. D-SERINE IS INVOLVED IN THE 
β-AMYLOID-RELATED PATHOPHYSIOLOGY IN ALZHEIMER’S DISEASE. 14eme Colloque de 
la Société des Neurosciences, May 2019, Marseille, France.  hal-02331616

HAL Id: hal-02331616
https://hal-normandie-univ.archives-ouvertes.fr/hal-02331616
Submitted on 24 Oct 2019

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.
Activation of N-methyl-D-aspartate subtype of glutamate receptors (NMDAR), key regulators of functional brain plasticity and memory process, requires the binding of the co-agonist D-serine. The homeostasis of these receptors are affected by soluble oligomers of the beta-amyloid peptide (Aβo) in Alzheimer’s disease (AD). Aβo toxic effects possibly pass through mechanisms involving D-serine since Aβo stimulates in vitro the production of the co-agonist. However, the actual in vivo contribution of D-serine in the functional NMDAR-related deregulations mediated by Aβo is still unknown.

In this study, we wonder if D-serine contributes in vivo to NMDAR deregulations mediated by Aβo. Behavioral analysis combined to extracellular electrophysiological recordings at hippocampal synapses is conducted in the 5xFAD transgenic mice model of amyloidogenesis displaying marked increase in Aβo rates. They are compared to 5xFAD animals in which the homozygous gene of the serine racemase (SR) that synthesizes D-serine, has been jointly invalidated.

Our results show that deletion of serine racemase prevents, at least partially, memory-related behavioral deficits observed in mice with prominent features of amyloidogenesis. Besides, impairment of NMDAR-dependent functional plasticity, indicated a significant contribution of D-serine in NMDAR-dependent β-amyloid related pathophysiology of AD.

D-SERINE IS INVOLVED IN THE β-AMYLOID-RELATED PATHOPHYSIOLOGY IN ALZHEIMER’S DISEASE

1Ploux E., Gorisse-Hussonnois L., 2Radzishevsky I., 2Wolosker H., 1Freret T., 1Billard J.-M.
1Normandie Univ, UNICAEN, INSERM, COMETE, GIP CYCERON, 14000 Caen, France
2Department of biochemistry, Technion, Israel Institute of Technology, Haifa, Israel

Contact : eva.ploux@unicaen.fr

Phenotype characterization
- Hippocampal Aβo levels 3-4-month-old mice (n=6 to 6 per group)
- Hippocampal D-serine levels 3-4 and 12 month-old mice (n=6 for all groups)

In vivo recordings at CA1 stratum radiatum hippocampal slices from either 3-4 or 10-12 month-old mice (after electrical stimulation of Schaffer collaterals)
- High frequency (100 Hz)-induced long-term potentiation (LTP)
- Testing stimulation (average of 3 stimulations at 0.1 Hz for 15min baseline and then resumed for 60 min after conditioning)
- Conditioning: 1 electrical train of stimulation at 100 Hz for 1 sec
- Isolated NMDAR-mediated fEPSPs (field excitatory postsynaptic potentials): fEPSPs were recorded and fEPSP/FPS ratio were calculated for Input/Output curves
- Recording were performed (low magnesium supplemented medium with the non-NMDAR antagonist NIKO, 10µM) either before and 15 min after addition of D-serine (100µM)

No genotype difference of NMDAR activation is observed in basal conditions (A)

Only WT and 5xFAD/SR-/- mice show significant D-serine-induced increase in NMDAR activation (B)

SIR deletion (5xFAD/SR-/-) reverses working memory deficits displayed by 5xFAD

SIR deletion (5xFAD/SR-/-) partially reverses reference memory deficits displayed by 5xFAD mice after a second spatial learning