D-serine is involved in the β-amyloid-related pathophysiology in Alzheimer's disease

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

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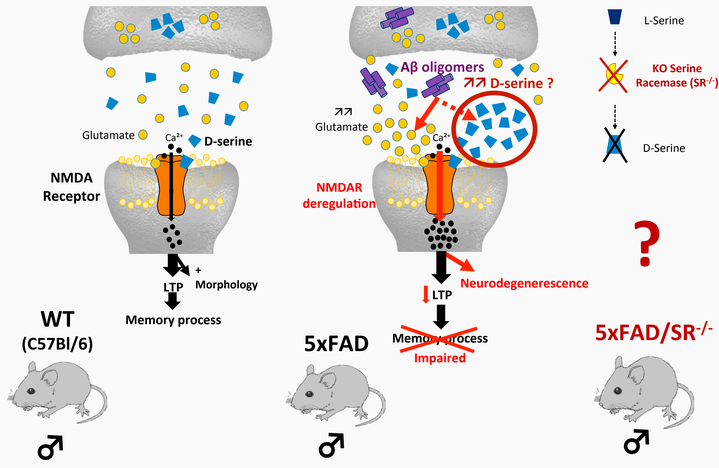
Activation of **N-methyl-D-aspartate subtype of glutamate receptors** (NMDAr), key regulators of functional brain plasticity and memory process, requires the binding of the **co-agonist D-serine**. The homeostasis of these receptors are affected by soluble **oligomers of the beta-amyloid peptide** (Aßo) in Alzheimer´s disease (AD). Aßo toxic effects possibly pass through mechanisms involving D-serine since Aßo stimulate *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 Aßo is still unknown.



In this study, we wonder if D-serine contributes *in vivo* to NMDAr deregulations mediated by Aßo. **Behavioral analysis** combined to **extracellular electrophysiological** recordings at hippocampal synapses is conducted in the **5xFAD transgenic mice model of amyloïdogenesis** displaying marked increase in Aßo 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 amyloïdogenesis. Besides, **impairment of NMDAr-dependent functional plasticity**, indicated a **significant contribution of D-serine** in NMDAr-dependent β-amyloid related pathophysiology of AD.

1 Phenotype characterization

- **Hippocampal $A\beta_{42}$ levels** 3-4 months old mice (n=4 to 6 per group)
- **Hippocampal D-serine levels** 3-4 and 12 month old mice (n=6 for all groups)

2 Electrophysiology

Extracellular recording in **CA1 *stratum radiatum* hippocampal slices from either 3-4 or 10-12 month-old mice** (after electrical stimulation of **Schaffer collaterals**)

- **High frequency (HFS)-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):**
- Presynaptic Fiber Volley (PFV) and field Excitatory Postsynaptic Potentials (fEPSPs) were recorded and fEPSP/PFV ratio were calculated for Input/Output curves
- Recording were performed (low magnesium supplemented medium with the non-NMDAr antagonist NBQX, 10µM) either **before** and 15 min **after addition of D-serine** (100 µM)

3 Behavioral characterization

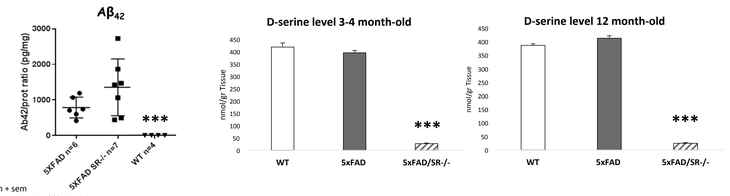
Spontaneous alternation test

- **12 month-old mice were tested for working memory** performances
- Mice were let free to explore Y-maze for 8-min and successive entry of the 3 arms of the maze was considered as an alternation
- The **percentage of alternation** was calculated as follows: NB of alternations / (total NB of arms visited – 2) x 100

Morris Water Maze

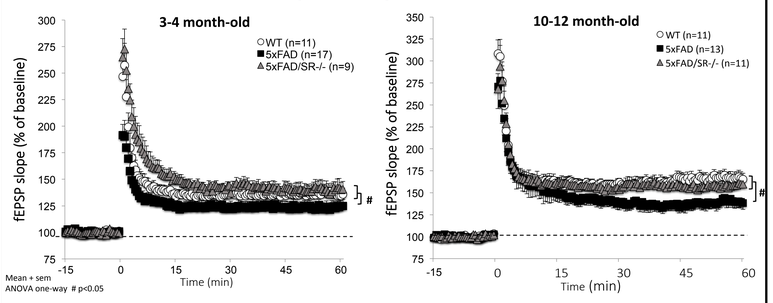
- **12 month-old mice** were trained to learn location of hidden platform (through distinct visual cues)
- **Learning** *(spatial learning performance)* and **relearning** *(flexibility)* session: 4 trials/day during 5 days (60 sec inter-trial interval)
- **Probe tests** (spatial reference memory performance): performed 48 after last trial of (respectively, learning and relearning session). Platform was removed and mice were free to explore the maze during 60 sec

1 Hippocampal phenotype of the experimental groups



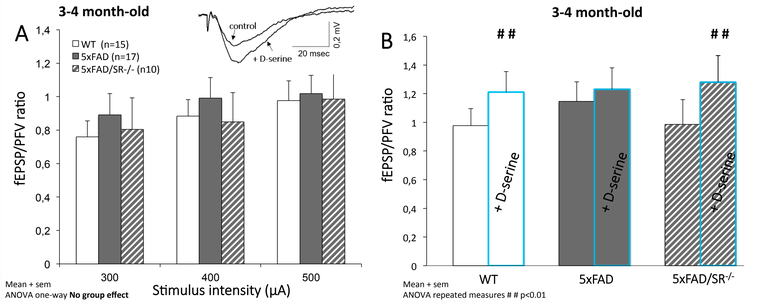
5xFAD and 5xFAD/SR$^{-/-}$ display **similar** hippocampal level of Aßo
(only traces were observed in WT mice, used as negative control)
5xFAD/SR$^{-/-}$ mice at both ages show markedly reduced hippocampal level of D-serine
(either compared to WT mice or 5xFAD)

2 Functional plasticity (HFS-induced LTP)



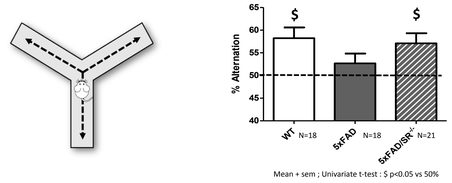
SR deletion (5xFAD/SR$^{-/-}$) reverses LTP deficits displayed in 5xFAD mice, both in 3-4 and 10-12 month-old animals

NMDAr activation (isolated synaptic potentials)



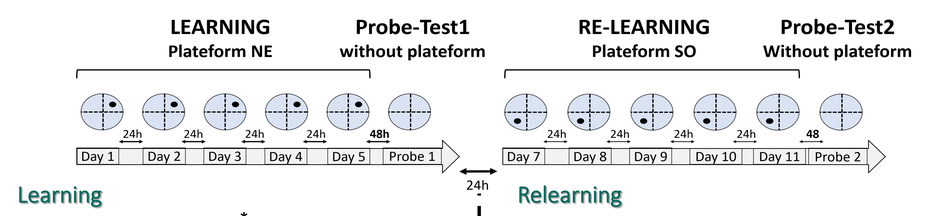
No genotype difference of NMDAr activation is observed in basal conditions (A)
Only WT and 5xFAD/SR$^{-/-}$ mice show significant D-serine-induced increase in NMDAr activation (B)

3 Working memory

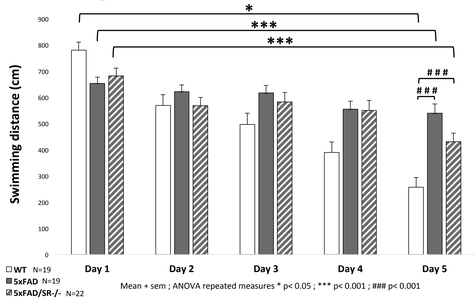


SR deletion (5xFAD/SR$^{-/-}$) reverses working memory deficits displayed by 5xFAD

Spatial learning, Flexibility, Reference memory

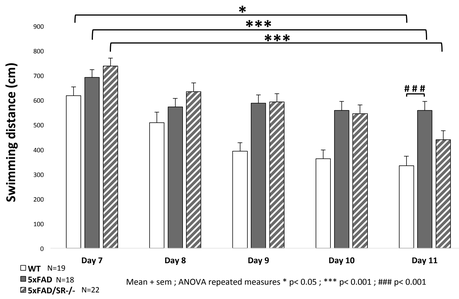


Learning



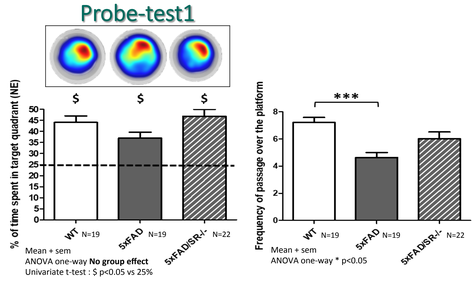
5xFAD and 5xFAD/SR$^{-/-}$ mice display reduced spatial learning performances (compared to WT mice)

Relearning

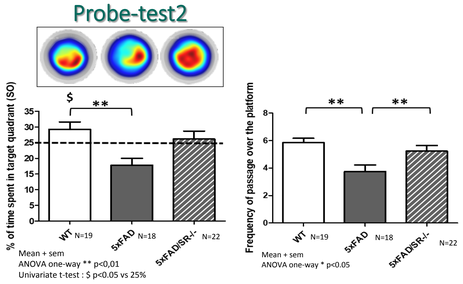


5xFAD mice display flexibility deficits (compared to WT mice), fully reversed in 5xFAD/SR$^{-/-}$ mice

Probe-test1



Probe-test2



Unaltered reference memory in 5xFAD and 5xFAD/SR$^{-/-}$ mice

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