IMPACT OF D-SERINE DEPLETION IN THE β-AMYLOID CASCADE RELATED TO ALZHEIMER'S DISEASE

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D-serine, as a co-agonist of N-methyl-D-aspartate subtype of glutamate receptors (NMDAR), is a key regulator of their activation. Hence, D-serine is involved in functional brain plasticity and memory processes. In the course of Alzheimer's disease (AD), homeostasis of NMDA receptors is precociously affected by beta-amyloid peptides (Aβ). However, while early functional dysregulations of NMDAR are well known, contribution of D-serine in early phases of the pathology remains so far to be determined. To this end, we compared behavioral performances and hippocampal synaptic functioning (extracellular electrophysiological recordings) in the well-known 5xFAD transgenic mice model of amyloidogenesis (bearing 5 familial Alzheimer disease-linked mutations), having or not a depletion for serine-racemase gene (allowing D-serine synthesize). Adequate control groups (WT and serine-racemase KO mice) were also performed.

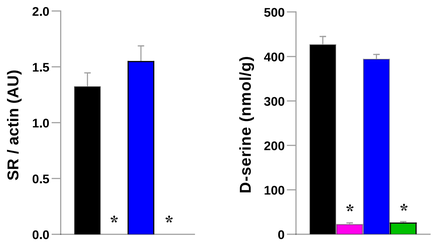
WT **SR$^{-/-}$** **5xFAD** **5xFADSR$^{-/-}$**

- ***All data expressed as mean + sem***
- Univariate t-test:
  - **$** p<0.05 vs 50%
  - **§** p<0.05 vs 25%
- ANOVA one-way: * p<0.05 vs WT
- ANOVA repeated measures: # p<0.05 vs WT

BIOCHEMICAL ANALYSES

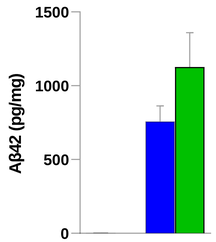
- 3-4 months old
- n = 3-7 per group

Hippocampal expression of Serine-racemase and D-serine level



No significant difference levels of D-serine were noticeable in 5xFAD mice (compared to WT).

Hippocampal $A\beta_{42}$ level

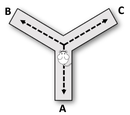


5xFAD and 5xFAD/SR-/- display similar hippocampal level of $A\beta_{42}$
(only traces were observed in WT and SR$^{-/-}$ mice)

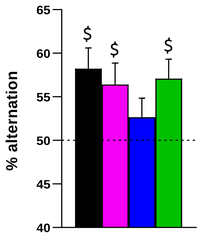
Behavior

- 10-12 months old
- n = 15-22 per group

Spontaneous alternation

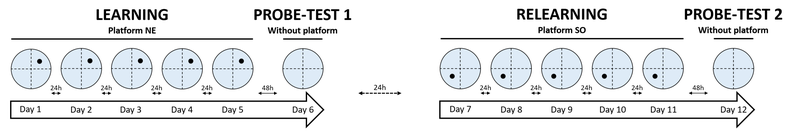


- Exploration in the Y-maze for 8-min
- Alternation = successive entries in the 3 arms
- Percentage of alternation
(compared to the chance value 50%)
NB of alternations / (total NB of arms visited – 2) x 100



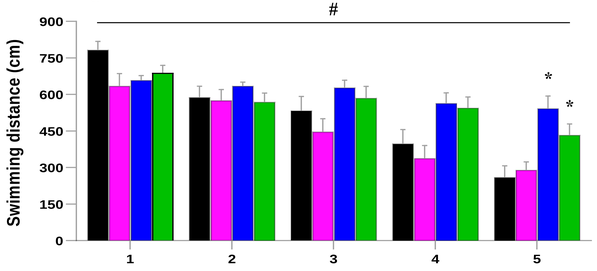
SR deletion in the bigenic mice reverses working memory deficits displayed by 5xFAD mice

Morris-water-maze

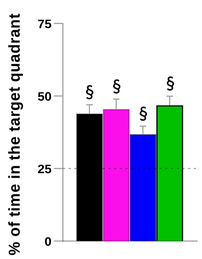


- Mice were trained to learn the location of the hidden platform (through distinct visual cues)
- **Learning** and **relearning** session: 4 trials of 60 sec / day during 5 days (60 sec inter-trial interval)
- **Probe tests**: 48 after last trial of learning and relearning session and mice were free to explore the maze without platform **during** 60 sec

Learning

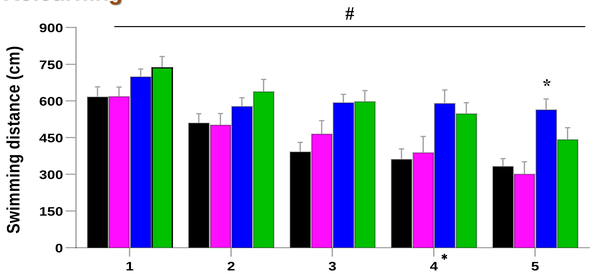


Probe-test 1

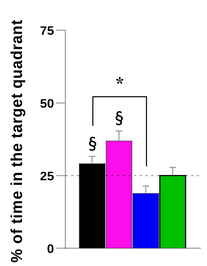


Compared to WT mice,
5xFAD and bigenic mice display reduced spatial learning performances,
but unaltered reference memory

Relearning



Probe-test 2



Compared to WT mice,
5xFAD mice display a flexibility deficit, noticeable during relearning and thus in the probe test.
Adding SR deletion alleviates this deficit during relearning
hence partially reverses reference memory deficits.

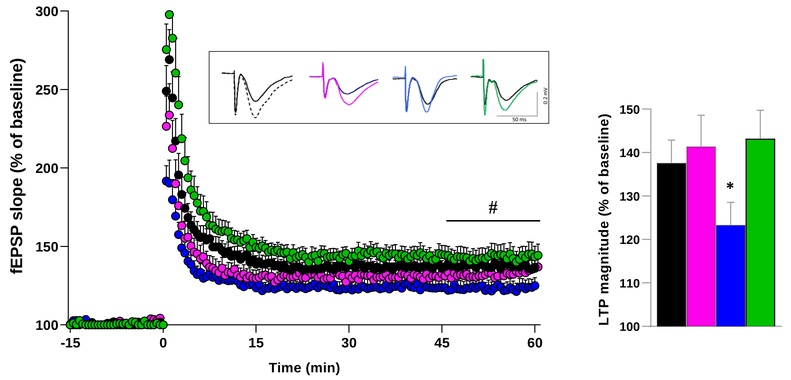
Ex vivo electrophysiological recording

- 3-4 months old
- n = 8-16 per group

Extracellular recording in **CA1 *stratum radiatum of* hippocampal slices**
(after electrical stimulation of **Schaffer collaterals**)

High frequency stimulation (HFS)-induced long-term potentiation (LTP)

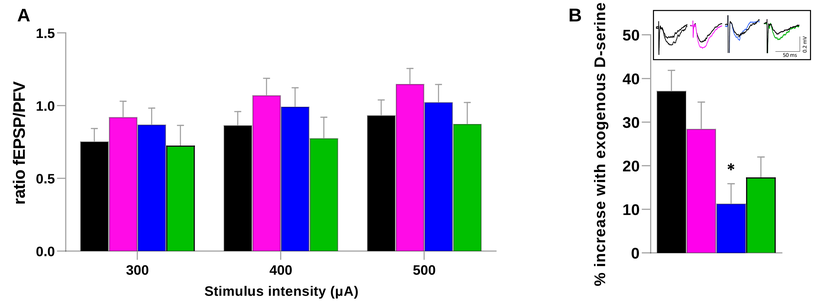
(1x100Hz)



SR deletion reverses LTP deficits displayed by 5xFAD mice

Isolated NMDAR-mediated fEPSPs (field Excitatory Post-Synaptic Potentials)

Presynaptic Fiber Volley (PFV) and fEPSPs were recorded in low magnesium supplemented medium with the non-NMDAr antagonist NBQX (10µM)
(A): Input/Output graph of fEPSP/PFV ratio (B): Percentage of increase of fEPSP/PFV ratio (at 300µA) either **before** and 15 min **after addition of D-serine**



(A) No genotype difference of NMDAR activation is observed in basal conditions
(B) The increase in NMDAR activation induced by exogenous-D-serine is significantly lower in 5xFAD mice, suggesting a decrease in NMDAR density, which is reversed when the SR is deleted concomitantly.

Altogether, these results highlight critical involvement of D-serine in Aβ-induced hippocampal network dysfunctions and related cognitive disabilities.

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