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D-SERINE CONTRIBUTES TO β -AMYLOID-DEPENDENT PATHOPHYSIOLOGY

IN ALZHEIMER'S DISEASE

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Key regulators of the structural and functional brain plasticity, the N-methyl-D-aspartate subtype of glutamate receptors (NMDARs) requires the binding of the co-agonist D-serine to be activated. In Alzheimer's disease (AD), soluble oligomers of the beta-amyloid peptide ($A\beta$) affect NMDARs possibly through mechanisms involving changes in D-serine levels since $A\beta$ stimulate *in vitro* the production of the co-agonist. In this study, we asked whether D-serine contributes *in vivo* to morpho-functional NMDAR-related deregulations mediated by $A\beta$. Behavioral analysis combined to electrophysiological recordings at CA1/CA3 hippocampal synapses have been thus conducted in the 5xFAD transgenic mice model of amyloidogenesis displaying marked increase in $A\beta$ rates and compared to 5xFAD animals in which the homozygous gene of the serine racemase (SR) that synthesizes D-serine, has been jointly invalidated.

EXPERIMENTAL PROCEDURES

- Behavioral analysis: 8-min spontaneous alternation test was performed in a Y maze apparatus to assess working memory performances in 10-12 months of aged mice. Successive entry of the three arms of the maze was considered as an alternation. The percentage of alternation was calculated as follows: number of alternations / (total number of arms visited - 2) x 100.
- Electrophysiology: Hippocampal slices (400 μ m thickness) were cut from two groups of WT, 5xFAD/SR^{+/+} and 5xFAD/SR^{-/-} mice aged 3-4 or 10-12 months. Field excitatory postsynaptic potentials (fEPSPs) and presynaptic fiber volley (PFV) were extracellularly recorded in CA1 stratum radiatum after electrical stimulation of Schaffer collaterals. Input/output curves of the fEPSP/PFV ratio of isolated NMDAR-mediated fEPSPs were constructed in a low magnesium medium supplemented with the non-NMDAR antagonist NBQX (10 μ M) before and 15 min after addition of D-serine (100 μ M). High frequency (HFS)-induced long-term potentiation (LTP) was studied in control medium after tetanic stimulation consisting in one train at 100 Hz delivered for 1 sec. Testing stimulation was then resumed for 60 min after HFS.
- Semi-quantitative immunoblotting analysis: Hippocampal tissue was homogenized in protein lysis buffer. The membranes were probed with antibodies against GluN1 (1:750), GluN2A (1:2500), GluN2B (1:800), GluA2 (1:500), serine racemase (1:400) or β -actin (1:7000). Proteins bands of interest were analyzed by scanning densitometry and normalized to β -actin density.

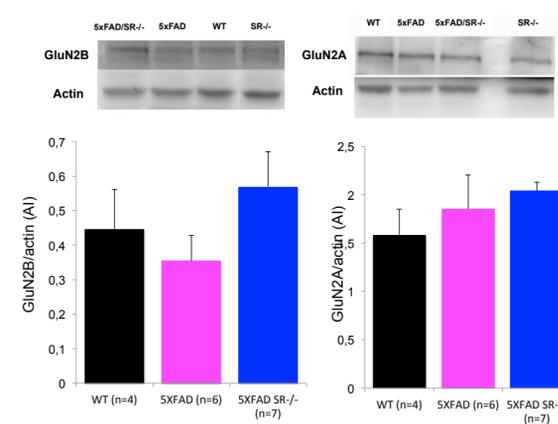
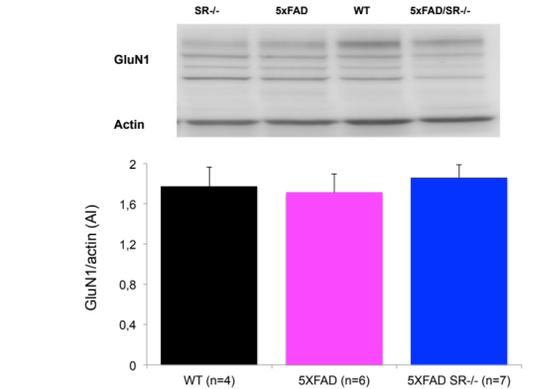
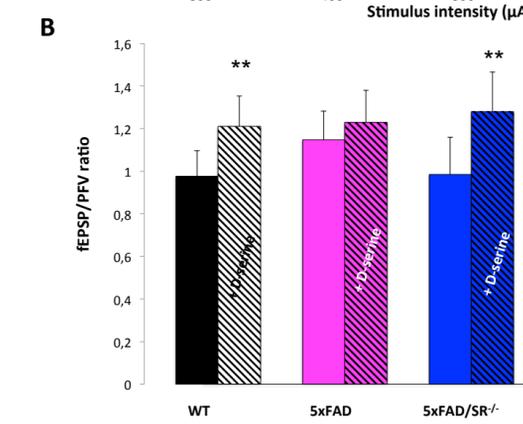
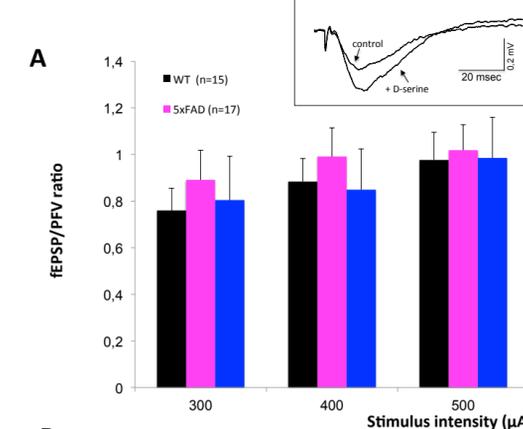
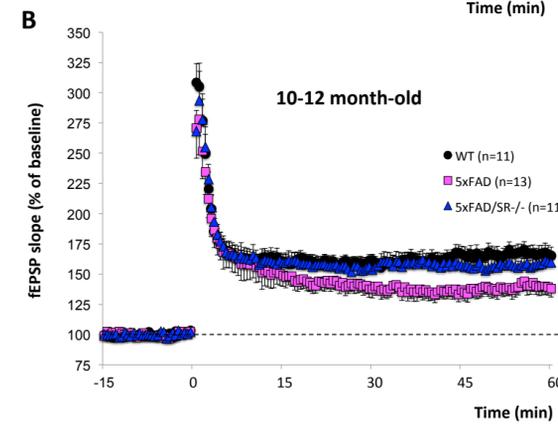
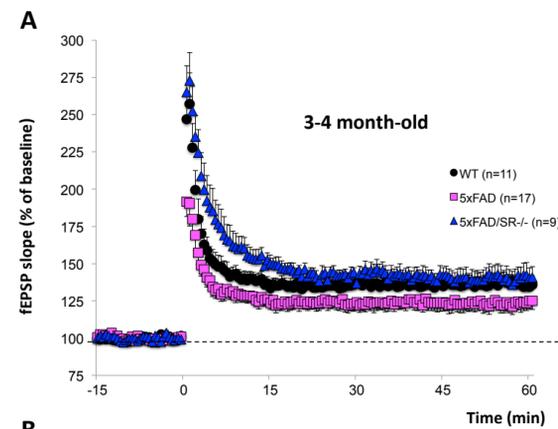
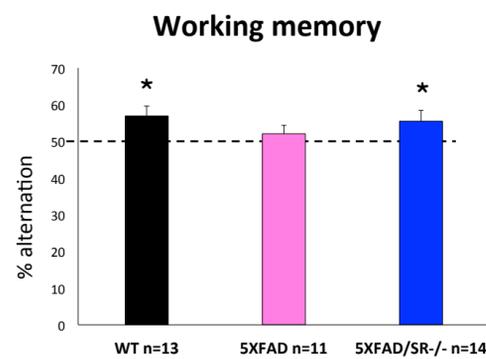
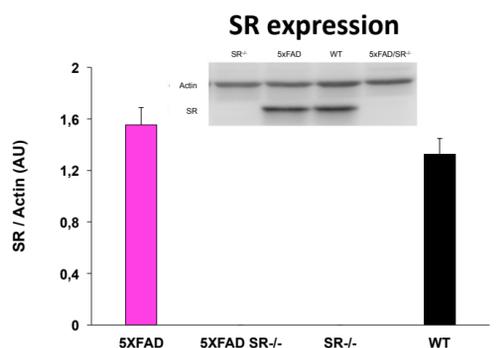
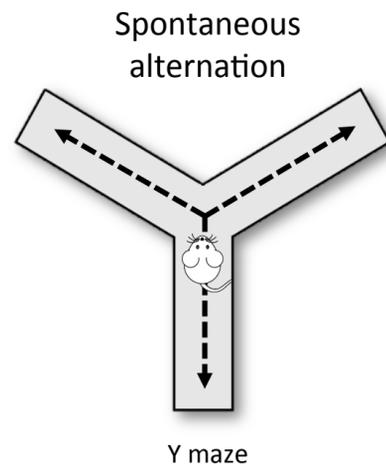
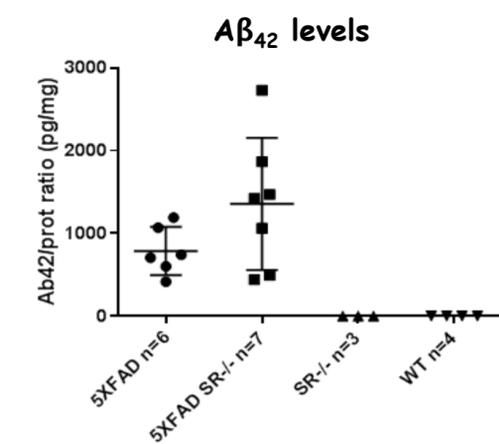
Hippocampal phenotype of the experimental groups

Behavioral analysis

Functional plasticity (HFS-induced LTP)

NMDAR activation (isolated synaptic potentials)

Protein expression



When in WT and SR^{-/-} mice displayed only traces of $A\beta$, significant levels are found in both 5xFAD and 5xFAD/SR^{-/-} animals

SR deletion reverses working memory deficits displayed by 5xFAD mice

SR deletion reverses LTP deficits displayed by both young (A) and aged (B) 5xFAD mice

Low frequency-induced NMDAR activation is similar in basal conditions in all experimental groups (A) but is significantly increased by exogenous D-serine only in WT and 5xFAD/SR^{-/-} mice (B)

Total protein expression for each NMDAR subunit is not significantly affected in 5xFAD mice although it is slightly decreased for GluN2B as compared to WT and 5xFAD/SR^{-/-} mice

Our results therefore show that deletion of serine racemase prevents memory-related behavioral deficits observed in mice with prominent features of amyloidogenesis as well as impairment of NMDAR-dependent functional plasticity, suggesting a significant contribution of D-serine in NMDAR-dependent β -amyloid-related pathophysiology of Alzheimer's disease.