D-SERINE CONTRIBUTES TO 
\(\beta\)-AMYLOID-DEPENDENT PATHOPHYSIOLOGY IN ALZHEIMER’S DISEASE

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Hippocampal of the serine racemase (SR) that synthesizes D-serine, has been jointly invalidated.

Behavioral analysis conducted in the 5xFAD transgenic mice model of amyloidogenesis displaying marked NMDAR-related deregulations mediated by Aβ0. Behavioral analysis combined to changes in D-serine levels since Aβ0 stimulate in vitro the production of the co-agonist D-serine to be activated. In Alzheimer's disease (AD), soluble oligomers of the beta-amyloid peptide (Aβ0) affect NMDARs possibly through mechanisms involving changes in D-serine levels since Aβ0 stimulate in vitro the production of the co-agonist D-serine to be activated.

In Alzheimer's disease (AD), soluble oligomers of the aspartate subtype of glutamate receptors (NMDARs) requires the binding of the co-agonist D-serine to be activated.

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 (Aβ0) affect NMDARs possibly through mechanisms involving changes in D-serine levels since Aβ0 stimulate in vitro the production of the co-agonist D-serine to be activated.

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.

EXPERIMENTAL PROCEDURES

1) 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.

2) Electrophysiology: Hippocampal slices (400 µm 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/PVF ratio of isolated NMDAR-mediated fEPSPs were constructed in a low magnesium medium supplemented with the non-NMDAR antagonist NBQX (10µM) before and 15 min after addition of D-serine (100 µM). 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.

3) 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 (1:400) or β-actin (1:7000). Proteins bands of interest were analyzed by scanning densitometry and normalized to β-actin density.

In WT and SR-/- mice displayed only traces of Aβ0, significant levels are found in both 5xFAD and 5xFAD/SR-/- animals.