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A ROBUST LINK BETWEEN D-SERINE AND AMYLOID PATHOLOGY IN A MOUSE MODEL

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N-methyl-D-aspartate receptor (NMDAr) plays a crucial role in neuronal plasticity and higher brain functions such as memory and learning. Its activation requires, additionally to glutamate, binding of a coagonist, such as D-serine. NMDAr are affected by the β-amyloid (Aβ) pathology and growing number of evidences suggest an involvement of D-serine in plasticity and cognitive-related impairments. Therefore, transgenic 5xFAD mice (bearing 5 familial Alzheimer disease-linked mutations) which shows accentuated amyloidogenesis, was crossed with mice having a deletion of the gene coding for Serine-Racemase (SR), converting L- into D-serine, to generate a bicianic line of mice: 5xFAD/SR⁻/⁻.

To assess the role of D-serine within Aβ-induced alterations, transgenic lines of mice (10-12 months old) were compared through a combined approach (gathering biochemical analyses, hippocampal-dependent behavioral tests and extracellular electrophysiological recordings at CA3/CA1 hippocampal synapses).

**Transgenic mouse line comparison**

- WT
- 5xFAD
- 5xFAD/SR⁻/⁻

Data are expressed in mean ± sem

- Univariate test: p<0.05 vs 5xFAD
- ANOVA one-way: * p<0.05 vs WT
- ANOVA repeated measures: & p<0.05 vs WT

**Behavior**

- **Spontaneous alternative test**
  - Morris Water Maze
  - Learning
  - Probe-test 1: 8 trials of 60 sec/day
  - Probe-test 2: 8 trials of 60 sec/day
  - Worst to best session: Platform was removed and mice were free to explore the whole maze during 60 sec.

- **Relearning**
  - Learning
  - Probe-test: 4 trials of 60 sec/day
  - Platform was removed and mice were free to explore the entire maze during 60 sec.

- No genotype difference of swimming distance was observed.

- No genotype difference of swimming distance was observed.

**Ex vivo electrophysiological recording**

- Extracellular recording in CA1 stratum radiatum of hippocampal slices
  - High frequency stimulation (HFS)-induced long-term potentiation (LTP)

**Biochemical analyses**

- Hippocampal expression of Serine-Racemase and D-serine level

  - No expression of Serine Racemase in SR⁻/⁻ and bicianic mice, agreeing with the very low level of D-serine in these lines.

  - Of note, higher levels of D-serine were noticeable in 5xFAD mice (compared to WT).

- Hippocampal Aβ₁₋₄₂ level

  - Slight – but non significant – decrease of Aβ₄₂ in bicianic mice (compared to 5xFAD)

**Results**

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