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## D-serine is involved in the $\beta$ -amyloid-related pathophysiology in Alzheimer's disease

E Ploux, L. Gorisse, I Radzishovsky, H Wolosker, T Freret, J-M Billard

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Contact :

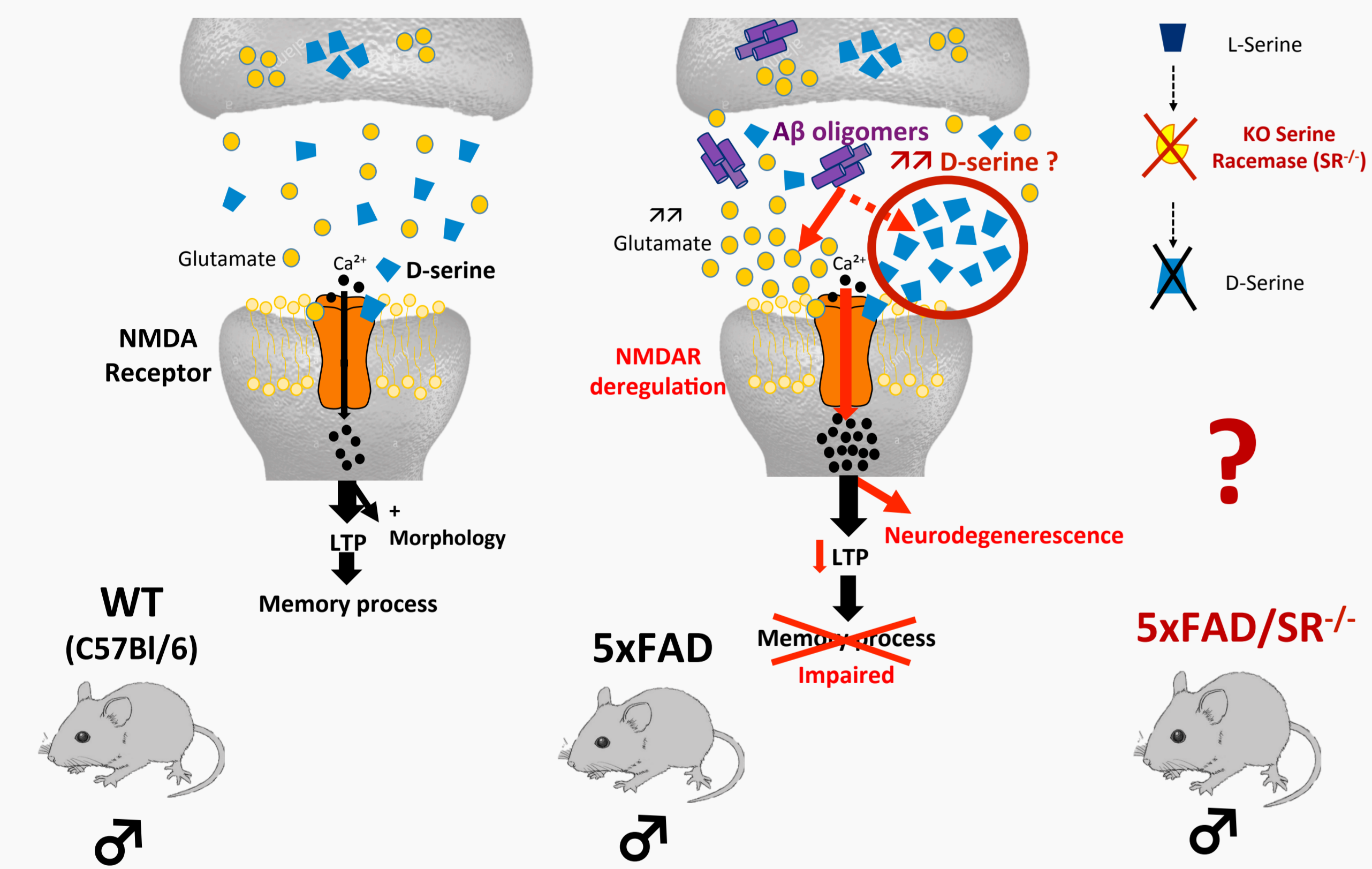
[eva.ploux@unicaen.fr](mailto:eva.ploux@unicaen.fr)

<sup>1</sup>Ploux E., Gorisse-Hussonnois L., <sup>2</sup>Radzishovsky I., <sup>2</sup>Wolosker H., <sup>1</sup>Freret T., <sup>1</sup>Billard J-M.

<sup>1</sup>Normandie Univ, UNICAEN, INSERM, COMETE, GIP CYCERON, 14000 Caen, France

<sup>2</sup>Department of biochemistry, Technion, Israel Institute of Technology, Haifa, Israel

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 (A $\beta$ )** in Alzheimer's disease (AD). A $\beta$  toxic effects possibly pass through mechanisms involving D-serine since A $\beta$  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 A $\beta$  is still unknown.



In this study, we wonder if D-serine contributes *in vivo* to NMDAR deregulations mediated by A $\beta$ . **Behavioral analysis** combined to **extracellular electrophysiological recordings** at hippocampal synapses is conducted in the **5x FAD transgenic mice model of amyloidogenesis** displaying marked increase in A $\beta$  rates. They are compared to 5x FAD 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 amyloidogenesis. Besides, **impairment of NMDAR-dependent functional plasticity**, indicated a **significant contribution of D-serine** in NMDAR-dependent  $\beta$ -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, 10 $\mu$ M) either **before** and 15 min **after addition of D-serine (100  $\mu$ M)**

### 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

