# Quantitative mechanistic model for amyloid beta and tau protein role in synaptic plasticity

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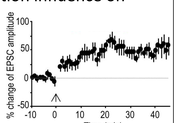
## INTRODUCTION AND AIMS

Amyloid beta (Aβ) and tau protein are both implicated in long-term potentiation (LTP) impairment and indicate early Alzheimer's disease (AD). It is still unknow how Aβ and tau phosphorylation influence on intracellular processes.

**Aims of the work are**

- to describe mouse and human LTP effect and tau phosphorylation on ex vivo data by mechanistic quantitative systems pharmacology model of AD pathology
- to simulate drug and washout of oAβ influence on extrasynaptic NMDA receptors with oAβ




pmid 21745645

## METHODS

**The QSP model** includes (pmid 27185535):

a) nACh and glutamate dependent systems (NMDARs are extrasynaptic and synaptic)

b) IP3R activation

c) Kinase/phosphatase complex

d) tau phosphorylation

e) **Aβ influence** on nAChr and glial uptake

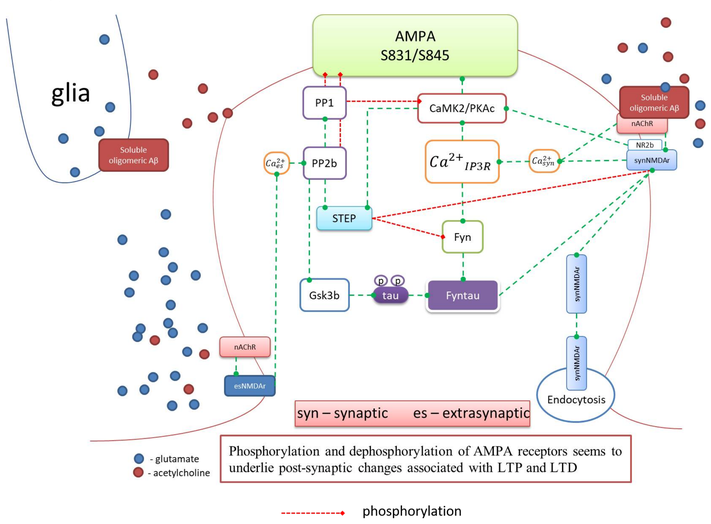



**Figure 1.** Scheme of synaptic plasticity model

## MODEL VALIDATION

Verification on acetylcholine and glutamate systems data (mice)

Synaptic plasticity verification on data with nAChr KO and stimulation of two systems (acetylcholine and glutamate) (pmid 21745645) (Fig.2)

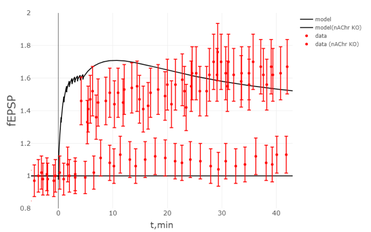



**Figure 2.** Synaptic plasticity model (black) and data (red)

Cholinergic and glutamate stimulation leads to influx of calcium in postsynapse, change of calcium dynamics depending of the timing of cholinergic input relative to glutamate input (Fig.2a)

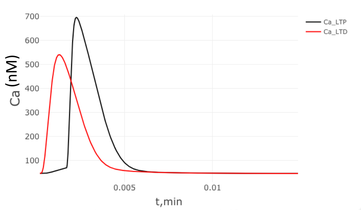



**Figure 2a.** Calcium dynamics at two different regimens (LTP and LTD)

Validation on NR2b (effect of antisense-NR2b treatment) and *tau-/-* rats and mice data

LTP effect of the model was validated on data for rats with antisense-NR2b (pmid 11978838)

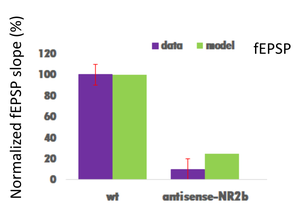



**Figure 3.** LTP effect model comparison with antisense-NR2b treatment data

LTP effect of the model was validated based on data for tau KO (tau-/-) mice (pmid 21289177)

$$\text{fEPSP slope} = \frac{Ser_{831} * Ser_{845}}{Baseline}$$

*In our model LTP (LTD) is ratio between phosphorylation of AMPAr to baseline of AMPAr*


**Figure 4.** LTP effect model comparison with tau-/- data

## RESULTS

fEPSP effect change differentially depending upon oAβ concentration; low-dose oAβ (4nM) **(Fig. 5(a))** and high-dose (400nM) **(Fig. 5(b))** (pmid 24027495)

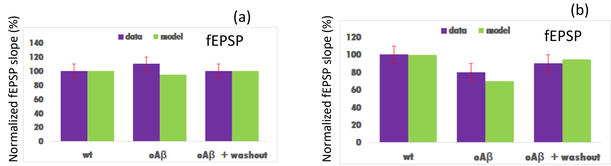



**Figure 5.** EPSP with low-dose of oAβ (a) and with high-dose of oAβ (b)

oAβ induce decrease of LTP (oAβ concentration is 42nM) **(Fig.6)** (pmid 20042680) and increase of tau phosphorylation (oAβ concentration is 500nM) **(Fig.7)** (pmid 23776240), but memantine leads to recovery of LTP and decrease of tau phosphorylation

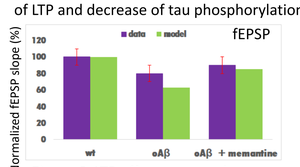



**Figure 6.** LTP effect recovers by memantine influence

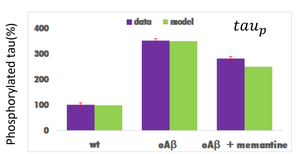



**Figure 7.** Tau phosphorylation is reduced by memantine influence

LTP and tau phosphorylation does not recovery with memantine (oAβ concentration is 1μM), but with combination memantine+washout is a complete rescue of LTP and decrease of tau phosphorylation (**Fig. 8,9**)

*MeM – memantine ; wsh - washout

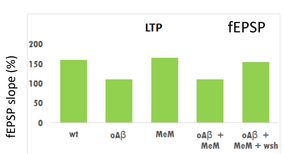



**Figure 8.** LTP effect with different conditions

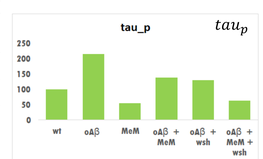



**Figure 9.** tau phosphorylation with different conditions

## CONCLUSIONS

- The model describes cholinergic and glutamate stimulation that leads to LTP;
- oAβ affect on LTP and tau phosphorylation increase;
- LTP recovers completely after washout of oAβ and with combination memantine + washout;
- LTP recovers from blockers impact on extrasynaptic NMDA receptors;
- tau phosphorylation decreases partially after memantine blockade of extrasynaptic NMDA receptors, or washout of oAβ, but not completely, and it approaches the normal concentration at treatment by combination memantine + washout;
- In perspective, this model can further be adapted for searching of optimal combination therapy targeting amyloid and synaptic processes.

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