Description of amyloid beta influence on synaptic plasticity and tau hyperphosphorylation by mechanistic quantitative systems pharmacology model

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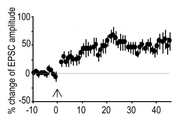
INTRODUCTION AND AIMS

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 hyperphosphorylation influence on intercellular processes.



pmid 21745645

Aims of the work are

- to describe mouse and human LTP effect and tau hyperphosphorylation data by mechanistic quantitative systems pharmacology model of AD pathology
- to simulate drugs influence on various mechanisms

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

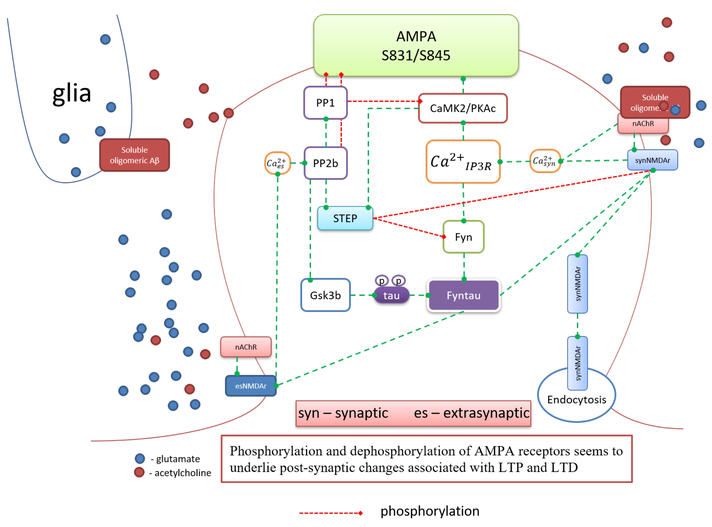


Figure 1. Scheme of synaptic plasticity model

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). LTP or LTD effects emerge seeing different calcium dynamics (input between acetylcholine and glutamate stimulation is 10ms or 100ms for LTP and LTD, respectively).

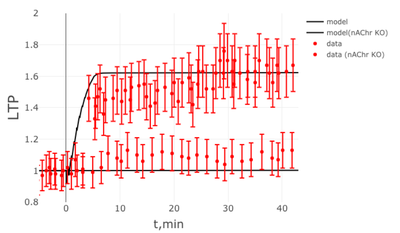


Figure 2. Synaptic plasticity model (black) and data (red)

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

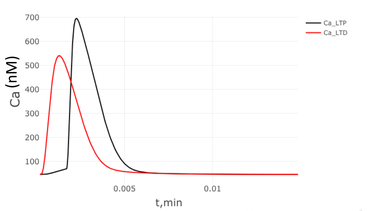


Figure 2a. Calcium dynamic in the two different regimen (LTP and LTD)

Validation on *Fyn-* and *tau-/-* mouse data

LTP effect of the model was validated based on data of mice with Fyn deficit (Fyn-) (pmid 9114065)

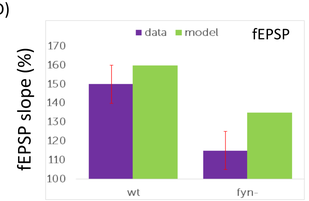


Figure 3. LTP effect model comparison with Fyn- data

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

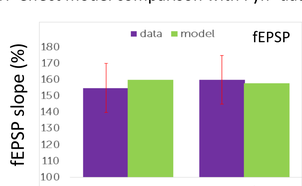


Figure 4. LTP effect model comparison with tau-/- data

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

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

RESULTS

Increase of calcineurin (PP2b) activity by oAβ impair synaptic placticity. Influence of inhibitor FK506 on PP2b reduce phosphates activity and recover of LTP (Fig. 5) (pmid 20544830)

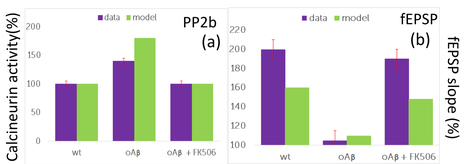


Figure 5. Calcineurin activity (a) and LTP (b) with oAβ and influence of FK506 inhibitor

oAb induce decrease of LTP, memantine leads to recovery of LTP (Fig.8) (pmid 27175329) and reduce tau phosphorylation (Fig.9) (pmid 23776240)

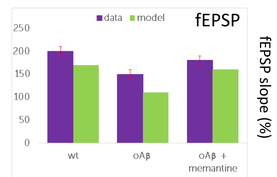


Figure 8. LTP recovers with influence of memantine on exNMDAr

SSR180711 (agonist of nAChr) led to a complete reversal of oAβ induced impairment of LTP (Fig.6) (pmid 23639920)

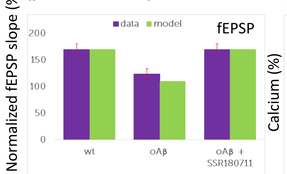


Figure 6. Effect of SSR180711 on oAβ mediated impairment of LTP

Influence of oAβ lead to excitotoxicity, but Fyn deficit recovers calcium to normal (Fig.7)

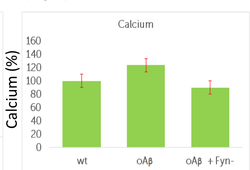


Figure 7. Peak of total calcium concentration

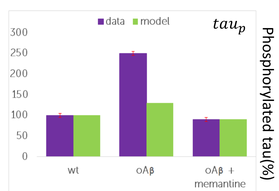


Figure 9. Tau phosphorylation is reduced by with memantine influence

CONCLUSIONS

- The model describes cholinergic and glutamate stimulation that leads to LTP or LTD, depending of the timing of cholinergic input relative to glutamate input;
- oAβ affect on LTP and tau phosphorylation increase;
- LTP impaired by oAβ recovers after PP2b inhibition;
- LTP recovers from blockers impact on extrasynaptic NMDA receptors and agonists influence on nACh receptors;
- In perspective, this model can further be adapted for searching of optimal therapy.

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