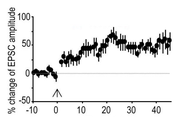
Quantitative systems pharmacology model of the effect of tau hyperphosphorylation on synaptic plasticity

Stepan Lerner, Tatiana Karelina

InSysBio, Moscow, Russia

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) OA influence on inhibition of PP (protein phosphates)
f) endocytosis of AMPAr

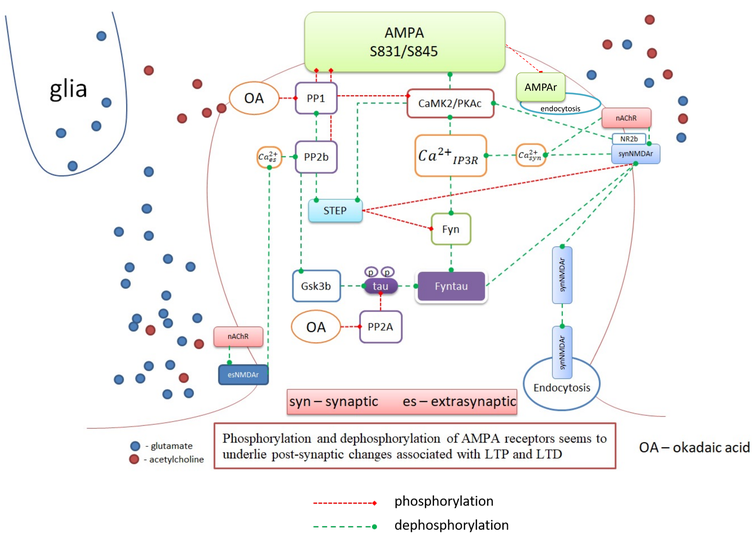


Figure 1. Scheme of synaptic plasticity model

MODEL VALIDATION

Verification on acetylcholine and glutamate systems data (mice)

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

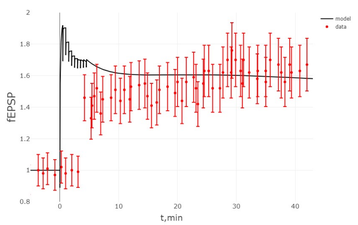


Figure 2. Synaptic plasticity model (black) and data (red)

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

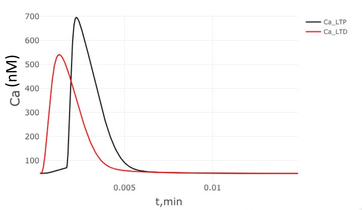


Figure 2a. Calcium dynamic in the two different regimen (LTP and LTD)

Validation on *calcium* and *LTP* data

Calcium dynamic of the model was validated based on data of mice with tau oligomers (Fig.3) (pmid 31918031)

Figure 3. Calcium model comparison with tau oligomers data

LTP effect of the model was validated based on data of mice with tau aggregation oligomers (Fig.4) (https://doi.org/10.1186/s13024-019-0326-4)

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

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

Figure 4. LTP effect model comparison with tau oligomers data

RESULTS

Anti-aggregant of tau, in contrast, even increased LTP relative to wild type (https://doi.org/10.1515/nf-2017-A063) (Fig.5)

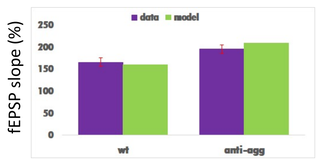


Figure 5. LTP with tau anti-aggregant

Lithium (inhibitor of Gsk3b) led to recovery of LTP (pmid 17241269) (Fig.6)

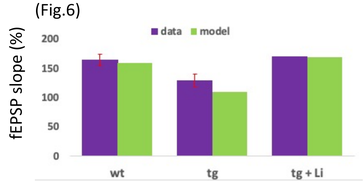


Figure 6. LTP effect recovers by lithium influence

The tau hyperphosphorylation was reduced to levels comparable with those detected in wild type (pmid 16803897) (Fig.7)

Okadaic acid induce decrease of LTP and increase tau phosphorylation, that anti-phosphopeptide antibody treatment has significantly decreased phosphorylated tau (Fig. 8) (pmid 27998769) and does not recovery of LTP (Fig. 9)

Figure 8. Tau phosphorylation with OA and influence of IgG

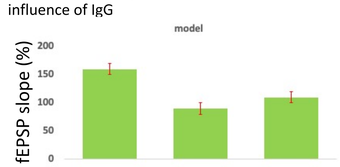


Figure 9. LTP with OA and influence of IgG

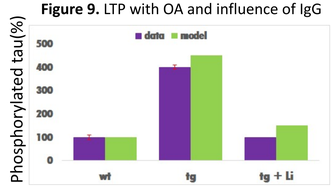


Figure 7. Tau phosphorylation is reduced by lithium influence

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;
- the description of synaptic processes proposed in the model provides a qualitative prediction of effects important for clinical trials;
- tau hyperphosphorylation decreases after Li inhibition of Gsk3b kinase. Also it declines under influence of IgG on tau and in the process of tau anti-aggregation;
- In perspective, this model can further be adapted for searching of optimal tauopathy therapy.

Stepan Lerner by e-mail: **lerner@insysbio.com**

www.insysbio.com