The QSP model of amyloid beta and tau oligomers influence on synaptic plasticity

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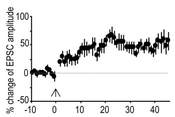
INTRODUCTION AND AIMS

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.



pmid 21745645

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 oAβ and otau influence on variation of MEP amplitude with iTBS stimulation

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) AMPAr endocytosis
f) Aβ influence on nAChr and glial uptake
g) otau influence on synaptic NMDAr and tau phosphorylation

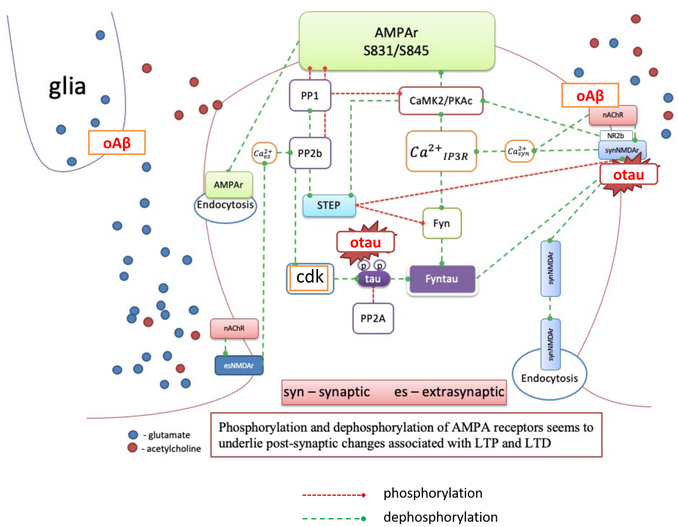


Figure 1. Scheme of synaptic plasticity model

MODEL VERIFICATION

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).

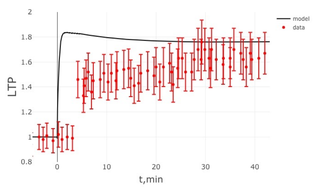


Figure 2. Synaptic plasticity model (black) and data (red)

LTP effect of the model was validated on ex-vivo data for tau oligomers (pmid 30120733) (Fig. 2a)

Figure 2a. LTP effect under the otau influence

Validation on AMPAr endocytosis (effect of NMDA application and with FK506) and ser845 phosphorylation on data cells

AMPAr endocytosis was validated on data for cell with application NMDA and NMDA + FK506* (pmid 11144360) (Fig. 3)

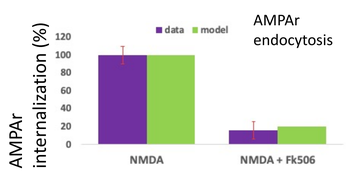


Figure 3. AMPAr endocytosis with NMDA and NMDA +FK506 application

Ser845 phosphorylation was validated on data with application NMDA and NMDA + Fk506* (pmid 11144360) (Fig. 4)

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

Ser_{845}; $Ser_{831_{845}}$ - receptor states
In our model LTP (LTD) is ratio between phosphorylation of AMPAr to baseline of AMPAr

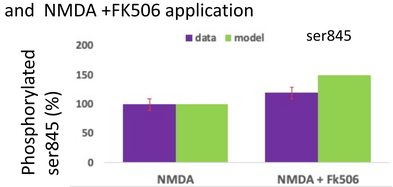


Figure 4. Phosphorylated ser845 with application NMDA and NMDA + Fk506

*FK506 – inhibitor of CaNA
*otau – tau oligomers

SIMULATION

SIMULATION FOR PATIENTS

MEP amplitude with iTBS protocol with low level of otau and high level of oAβ showed the expected absence of LTP. MEP with high level of otau and low level of oAβ showed a clear reversal of LTP to LTD **(Fig. 5)** (pmid 26757193). Values of oAβ and otau was taken from big integral model and are given in accordance with CSF (pmid 33818905)

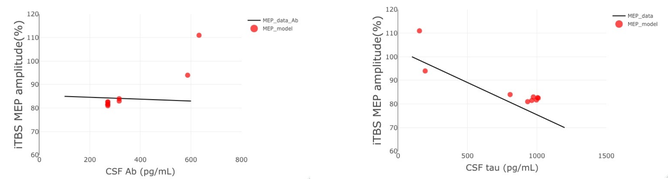


Figure 5. iTBS MEP amplitude with low and high levels of oAβ and otau

SIMULATION FOR MEMANTINE

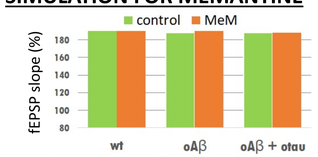


Figure 6. LTP effect with low concentration of oAβ and otau

Phosphorylated tau does not decrease with low concentration of oAβ (0.5nM) and otau (5nM) under the influence of memantine (10μM) **(Fig. 8)**

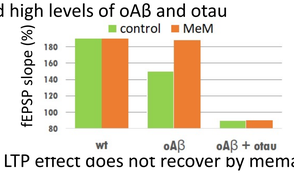


Figure 7. LTP effect does not recover by memantine influence (high concentration oAβ (5nM) and otau (116nM))

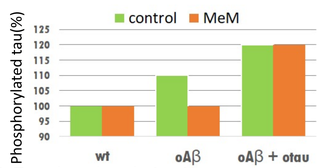


Figure 8. Tau phosphorylation is not reduced by memantine influence

*MeM – memantine

CONCLUSIONS

- The model describes cholinergic-glutamate and iTBS stimulations that leads to LTP;
- Low level of oAβ and high level of otau lead to reversal of LTP to LTD;
- Low level of otau and high level of oAβ lead to LTP absence;
- LTP does not recover after blocking of extrasynaptic NMDA receptors with high concentration of oAβ and otau;
- Memantine protect tau from oAβ induced tau hyperphosphorylation, but under the influence of otau on the system memantine is not "survive" normal phosphorylated tau level;
- In perspective this model can further be adapted for searching of optimal combination of therapy targeting amyloid and synaptic processes.

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