Quantitative systems pharmacology model of key intraneuronal pathways regulating toxic protein accumulation in Alzheimer's disease

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Background

Alzheimer's disease (AD) is a complex neurodegenerative disorder. Most known hallmarks of AD are accumulation of amyloid β (Aβ) and hyperphosphorylated protein tau. Apart from protein aggregate accumulation there are many intracellular processes altered in AD brain, which are related to Aβ and tau pathology, and are believed to be the cause or contributors to toxicity. The goal of this study was to develop a QSP model describing the key neuronal processes observed to be affected in AD and potentially influencing, or significantly influenced by, tau and Aβ pathology.

Methods

Modules:

- Sphingolipid metabolism: influences Aβ production, affected in AD
- Cholesterol metabolism: affected in AD
- Autophagic-lysosomal system (ALS): contributes to Aβ production, Aβ and tau degradation, affected in AD
- Other proteolytic systems: influence degradation and aggregation, affected in AD
- Exosome release: influences aggregation and propagation, affected in AD

Expressions for compounds:

- ODE-described variables
- QSS-derived functions

Regulation:

- Across modules
- From pathology drivers

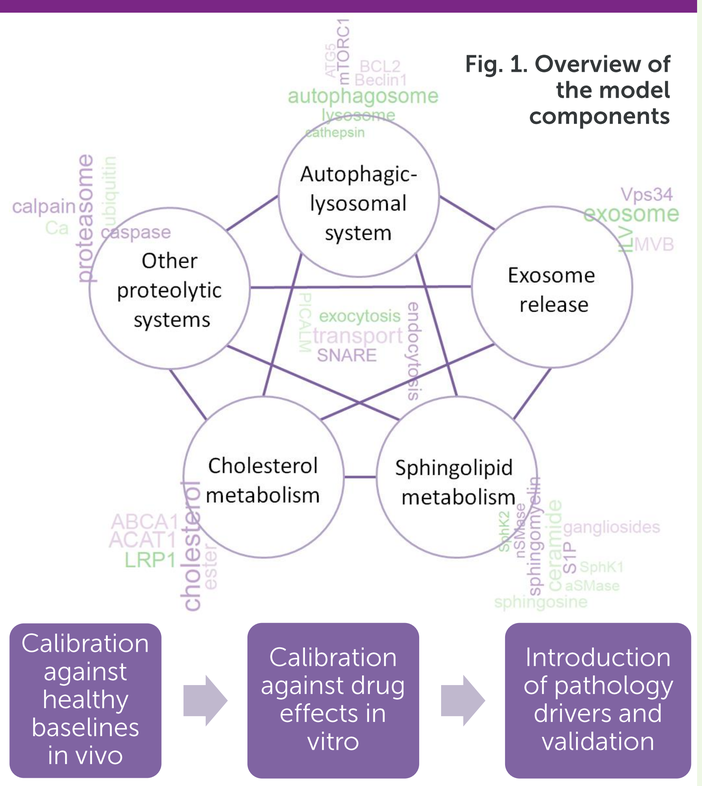


Fig. 1. Overview of the model components

Fig. 2. Process of model calibration and validation

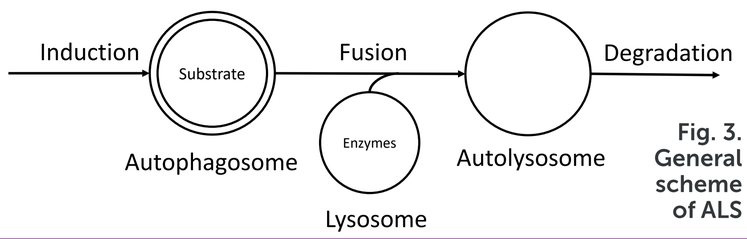


Fig. 3. General scheme of ALS

Results

Fitting of healthy baselines against in vivo human data:

- Sphingolipids [nM]
- Cholesterol [nM]
- Ubiquitin species [nM]
- ALS-related vesicles [relative volume]

Calibration against in vitro drug effects:

- Inhibitors and activators of different autophagy stages
- Inhibitors of enzymes involved in lipid metabolism
- Drugs affecting transport systems
- Drugs affecting ubiquitin-proteasome system

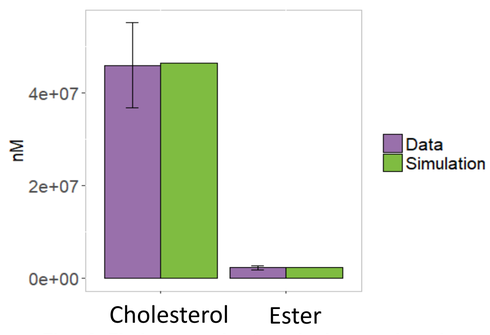


Fig. 4. Fitting results for cholesterol and cholesterol ester in human brain [1]

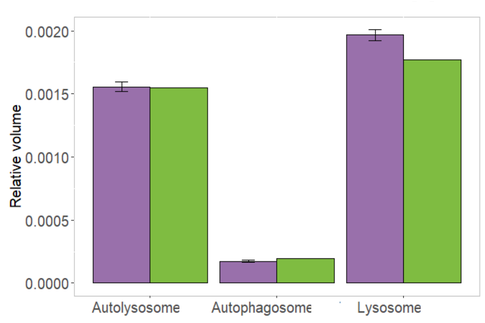


Fig. 5. Fitting result for ALS components in healthy human brain (values expressed in absolute vesicle volume divided by the volume of compartment) [2]

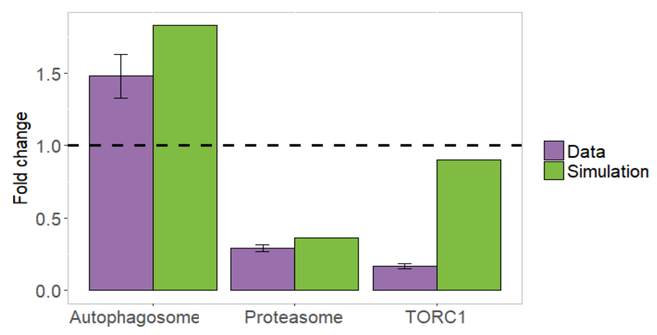


Fig. 6. Effect of proteasome inhibitor on ALS in the model compared to data [3]

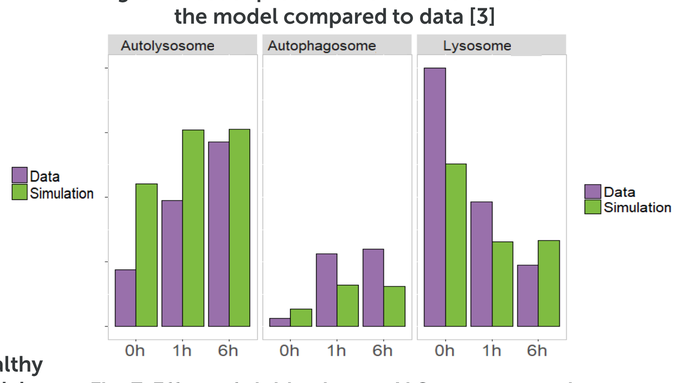


Fig. 7. Effect of vinblastine on ALS components in the model compared to data [4]

Potential disease drivers selected in the model are:

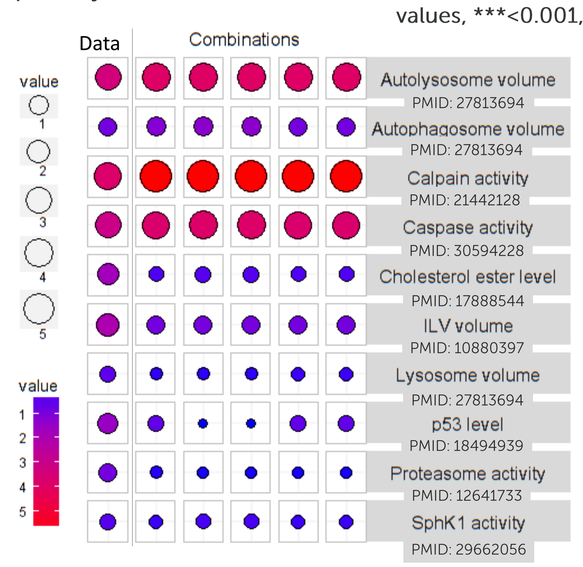
- From different cellular pathways (see fig. 1)
- Not likely to be downstream of tau and Aβ (inferred from data on transgenic mice)
- Detected in early stage

In vivo data on relationship AD vs control for various markers (see list in fig. 11) were used to estimate driver influence on the system

$$MSE = \frac{1}{n_{markers}} \sum_{markers} \left(\frac{AD_{model}}{Health_{model}} - \frac{AD_{data}}{Health_{data}} \right)^2$$

Fig. 8. Algorithm of driver contribution analysis (right) and formula for MSE calculation (left)

Fig. 9. Effects of different drivers on MSE. The smaller is MSE the closer is the model to experimental data. Green - all combinations with given driver, purple – without. SphK2 (sphingosine kinase 2) generally represents the pathway of calcium release from the ER, which leads to calpain activation. Asterisks indicate Wilcoxon test p-values, ***<0.001, **<0.01, *<0.05



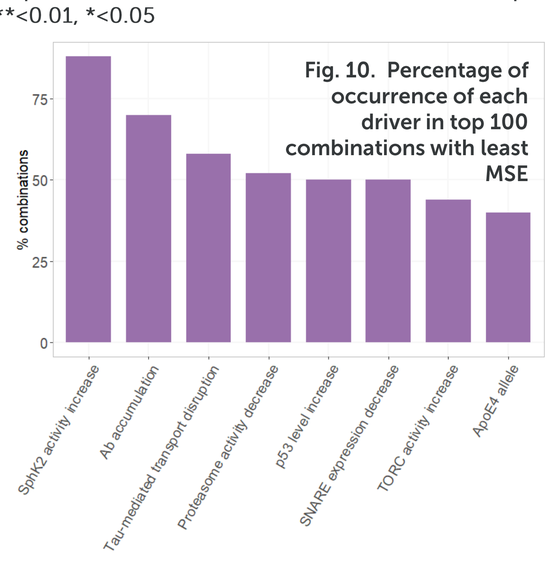


Fig. 10. Percentage of occurrence of each driver in top 100 combinations with least MSE

Fig. 11. AD/health ratios of selected markers according to experimental data and top 5 driver combinations with least MSE simulated in the model (color and size represent ratio value). All 5 combinations include Aβ, transport and SphK2 , and TORC1 , p53 in all except 3rd and 4th , SNARE is absent in all combinations, proteasome is present only in last one, and ApoE in 1st , 3rd and 5th

Conclusions

- The model describes key intraneuronal metabolic pathways, quantitatively corresponding to baseline healthy levels of different cellular components. Effect of diverse drugs and Aβ on the system reflects experimental data.
- Introduction of different drivers allows for correct description of neuron homeostasis pathology in AD, i.e. interrupted ALS flux, activated calpains and caspases, disbalance of cholesterol metabolism etc.
- Model can be used as a tool for mechanistic hypothesis generation for processes driving accumulation of toxic proteins in AD and testing potential driver contributions
- The most efficient disease drivers in the model are Aβ accumulation, disruption of transport due to tau-related abnormalities and activation of SphK2.

References

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