In silico modeling of alpha-synuclein oligomerization effects on neuronal homeostasis

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Abstract

Alpha-synuclein (ASYN) is a neuronal presynaptic protein critical for the pathogenesis of Parkinson's Disease (PD). Mutations in the gene encoding for ASYN have been shown to cause familial PD. Importantly, multiplications of the gene locus containing ASYN have also been directly linked with PD, suggesting that the levels of ASYN are crucial for neuronal homeostasis. Moreover, we have shown that overexpression of even the Wild Type (WT) of ASYN in differentiated SH-SY5Y neuroblastoma cells leads to cell death. This is correlated with the disruption of proteolytic machineries, prominently the CMA lysosomal pathway, caused by ASYN and the accumulation of ASYN oligomeric species (and not aggregates). Main role on the inhibition of CMA is also played by the modification of WT ASYN by Dopamine (DA), which is also considered to cause inhibition of the aggregation of ASYN and the subsequent accumulation of oligomers and to have a causal role to the cell loss. Since the critical balance in the levels of intracellular ASYN necessary to cause such dysregulations is unknown and many crucial aspects of the system are still not answered we initiate the creation of a systems biology oriented mathematical model targeting to assist the biological research by predicting the dynamics of the system and by testing hypotheses sufficient to motivate new experiments. Upon calibration based on existing biological knowledge and biochemical quantitative measurements available in our lab, the derived model is able to simulate the dynamics of ASYN expression and oligomerization and the basic lysosomal, macroautophagic and proteasomal biological pathways involved in the aberrant function of intracellular ASYN in combination with the contribution of DA to it. The developed biomodel was described in SBML with Cell Designer and it was Stochastically Simulated with COPASI. The parameters of the model were in part inferred from existing biomodels, adjusted, either by fine tuning or by the most established parameter estimation methods, to fit qualitative knowledge and quantitative data. It is worth mentioning that after the establishment of the model, in silico testing of hypotheses matched the conclusions of related in vivo experiments, not a priori known to the calibration of the model, (e.g. overexpressing the lysosomal receptor Lamp2a or reducing the DA production rate, lead to disappearance of oligomers), thus providing evidence for the correctness and the usefulness of the model.