Quantitative systems pharmacology modelling of Parkinson's disease for determining target suitability

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Parkinson's disease (PD) is a progressive neurodegenerative disease with no disease-modifying therapies so far. Multiple factors such as ageing, environment and genetics contribute to neurodegeneration and dopamine deficiency in PD. Mathematical modelling can help understand such complex multifactorial neurological diseases (1,2).

Aims

We aim to determine suitability of various PD targets using quantitative systems pharmacology (QSP) approach. For this purpose, we have constructed a QSP model of PD with a focus on mechanistic molecular machinery responsible for PD pathogenesis. The model is extended to simulate spatial PD propagation through the brain through diffusion of extra-cellular Asyn species. Challenging this model using hypothetical monoclonal antibodies (mABs) against various targets is expected to give insight into target suitability.

Methods

The model is informed by previously-published models of Asyn aggregation and its feedback with oxidative stress (3,4). These models are integrated with each other and combined with novel elements of Asyn secretion and reuptake. Further, diffusion of misfolded Asyn through the brain is included. The combined ordinary and partial differential equation model of PD is coded using method of lines (5) and simulated with Matlab. The resultant model is verified using various clinical data and subjected to hypothetical monoclonal antibody drugs against selected targets to quantify disease attenuation.

Results / Conclusions

The naïve PD model (i.e. in absence of drugs) displays existence of two steady states – one with low Asyn misfolding and low oxidative stress – presumed to be the healthy state, and the other with high Asyn misfolding and high oxidative stress – presumed to be the diseased state. Switching of healthy to diseased state can occur due to excess misfolded Asyn accumulation. The model also predicts spatial PD propagation due to the diffusion and cellular uptake of Asyn. Antagonizing various potential drug targets results in differential level of disease attenuation, thus allowing us to rank targets in their order of suitability. This exercise is expected to inform drug discovery efforts.

References:

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