QSP Modelling of Neurodegenerative Chronic Diseases and Brain Biomarkers: Adding the Effect of Ageing on Brain Volume

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Abstract

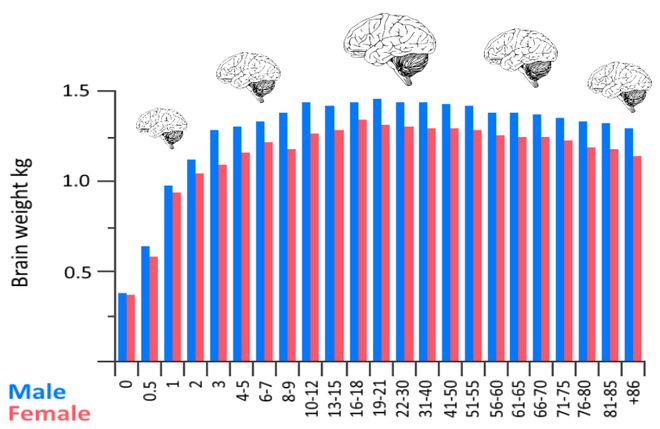
Given the complexity of neurodegenerative chronic diseases, e.g. **Alzheimer's,** there are still several challenges for the development of mechanistic models in drug development. In particular considering factors like "ageing" become important when analysing clinical data related to an elderly population. In order to include this additional dynamic factor, the objectives of this work are:

- Developing a new Quantitative Systems Pharmacology (QSP) modelling methodology considering brain volume changes for the estimation of biomarker concentrations.
- Comparing the results of a model with variable brain volume with a model using constant volume.
- Evaluating the effect of the variability of brain volume changes in a given population on the estimation of biomarker concentrations.

Background

Physiological modelling and simulation including brain physiology (and/or pharmacology) have been typically based on the assumption that brain is a constant volume. However, several studies have shown that the volume of the brain is not constant during the life of a person, being fully developed around 20 years and starting to decrease after this age [1] (see Figure 1).

Figure 1. Brain size for males and females over age [1]

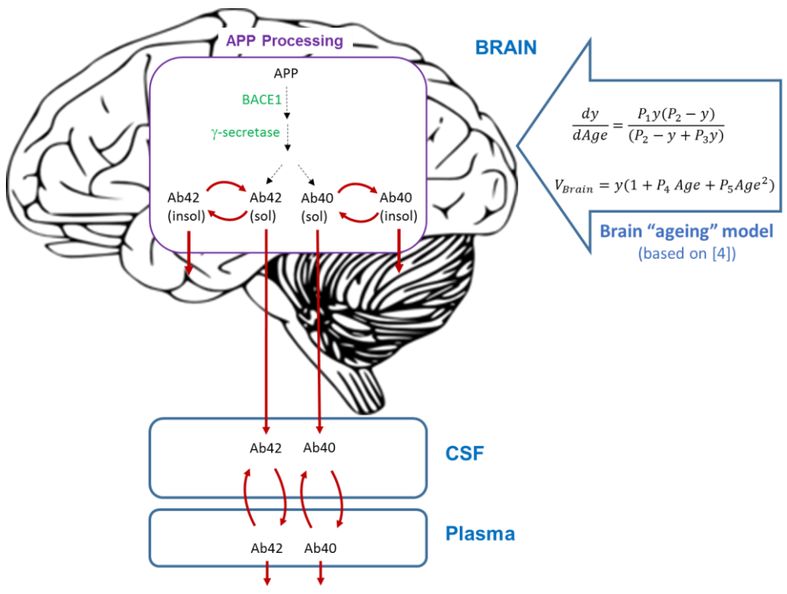


When studying neurodegenerative chronic diseases, e.g. Alzheimer's disease, changes in brain volume, either growth during brain development or decrease during adulthood and later ages, becomes quite important in the estimation of the concentration of specific biomarkers in brain, e.g. amyloid beta, cholesterol, etc.

Methods

The methodology proposed includes the implementation of a Quantitative Systems Pharmacology (QSP) model describing the main mechanisms related to Amyloid Precursor Protein (APP) processing and amyloid-beta (Aβ) production and accumulation in brain [2,3] in combination with an "ageing" model considering the effects of ageing on the variations (i.e. decrease) in the brain volume. The model was implemented in *Matlab/Simbiology* version 2017b (The Mathworks Inc., Natick, USA) as the flexibility of this modelling software allows the modeller adding the additional feature of variable volume in an easy and user-friendly way. The model was simulated using a stiff ODE (ordinary differential equation) solver (ode15s) given the different time scales needed to be considered and the time span being simulated (several decades of a patient live).

Figure 2. Simplified diagram of the QSP model for Neurodegenerative Chronic Diseases



To evaluate the variability of brain volume changes in a given population, the model was evaluated for three different virtual populations, i.e. only male, only female and mixed (50% males and 50% females) populations, simulating the dynamic biomarker changes for each of them.

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Results

The integrated Quantitative Systems Pharmacology (QSP) model shows sensible simulation results when comparing with clinical data published in the literature. When studying the accumulation of specific biomarkers (e.g. amyloid-beta), using a dynamic model which considers the lifespan of a patient and his brain volume change because of ageing, allows seeing how the decrease in brain volume can be related to the increasing concentration levels observed in the clinic.

Figure 3. Simulation results for Brain Volume and Comparison with Literature data. Results for Male (A), Female (B) and Mixed populations (C).

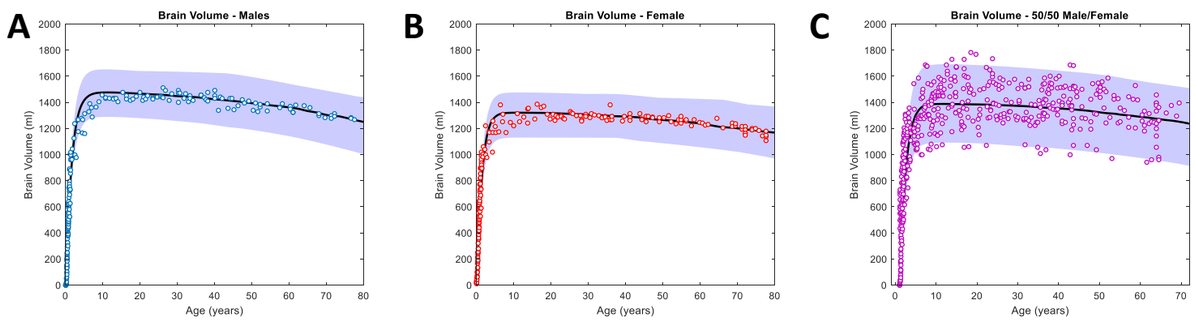
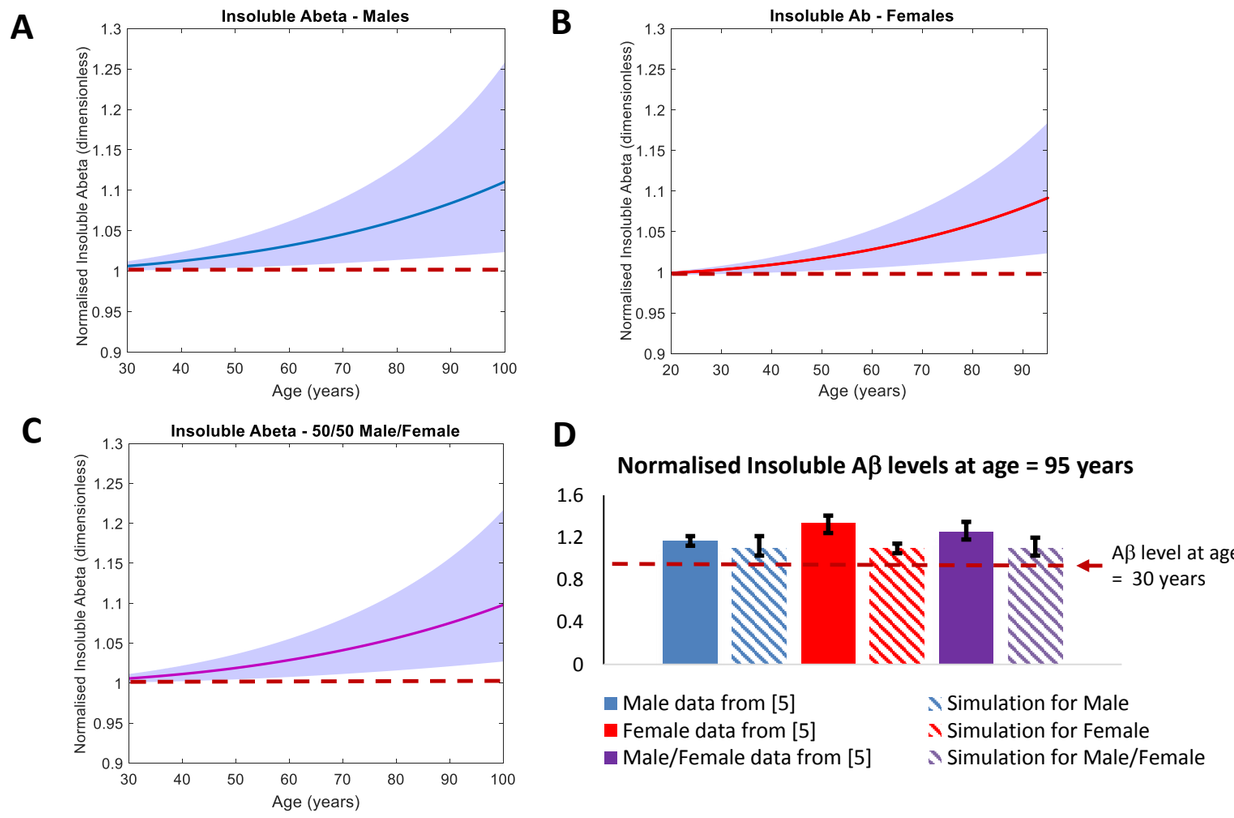


Figure 4. Simulation of Brain Insoluble Aβ levels: (A-C) Results for Male, Female and Mixed populations and comparison with "constant brain" model (dotted red line); (D) Comparison with trends reported in [5].



Conclusions

Simulation results from the integrated Quantitative Systems Pharmacology (QSP) model proposed suggest that the inclusion of a variable brain volume can help to have a better dynamic description of neurodegenerative chronic diseases in ageing populations and also to have a better estimation of biomarker concentration levels in this specific tissue.

References

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