QSP Model of Aß Accumulation Predicts Different Treatment Effects at Different Stages of Alzheimer's Disease

Objectives: We aimed to develop a representation of Aβ aggregation dynamics that recapitulates the characteristic "S-curve" observed in longitudinal studies; slow, accelerating growth at disease onset, reaching a period of constant growth, followed by a period of deceleration and eventually zero growth. Such a model would facilitate evaluation of treatment strategies at every stage of Aβ aggregation, from preventative or very early to late-stage therapeutic interventions.

Methods: We have previously developed a model of Aβ accumulation across the linear portion of its progression profile, as determined by substrate uptake value ratios (SUVR) acquired by PET imaging. This period spans from the prodromal disease stage, characterized by normal cognitive function with an SUVR above the threshold of Aβ positivity, through to the onset of dementia. Over this time frame, Aβ aggregation rates were well described by a linear function of Aβ42 and Aβ40 monomer concentration. To achieve the "S-curve" dynamic, Aβ rate equations were modified to achieve an initially slow but accelerating aggregation rate by introduction of a second-order saturating effect, Aβ monomers binding to previously formed fibrillar structures. This is analogous to the kinetics observed in in vitro experiments during the nucleation and elongation phases. To achieve the observed deceleration in plaque growth in later disease stage, when Aβ plaque mass approaches its maximal level, we introduced neuronal atrophy to the model to decrease the level of Aβ production in late-stage disease leading to a deceleration in the rate of plaque growth.

Results: The implemented mechanisms successfully capture the observed kinetics of Aβ accumulation across the entire continuum of disease progression, from the earliest pre-clinical years of pre-Aβ positivity through to late-stage dementia. A hypothetical therapy that reduces Aβ monomers was shown to be more impactful when given in the pre-prodromal stage than when given during the linear progression stage.

Conclusions: This expanded representation of Aβ accumulation widens our view into the critical process of disease etiology and extends the model's utility to support research and development of therapeutic interventions aimed at prevention or delay of Aβ plaque progression.

Authors

- Christina Friedrich, Rosa & Co (Presenting Author)
- Robert Sheehan, Rosa & Co (CoAuthor)
- Colleen M Witt, Rosa & Co (CoAuthor)
- Krishnakant Dasika, Rosa & Co (CoAuthor)

Reference: ACoP13 (2022) QSP-483 [www.go-acop.org/?abstract=483]
Quantitative Systems Pharmacology