INFORMATION OF DOCTORAL DISSERTATION

Title: **STUDY OF EFFECT OF MUTATIONS ON STRUCTURE AND DYNAMICS OF AMYLOID BETA PEPTIDES: IMPLICATIONS FOR ALZHEIMER'S DISEASE**

Major: **Engineering Physics**

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Abstract:

Alzheimer's disease (AD) is a brain impairment disease and a major cause of dementia in humans. AD is thought to be involved in the decline of neurons and synapses in the brain. Ever since AD was discovered, the cause of AD has not been determined exactly, but there are three main hypotheses: cholinergic, protein tau and amyloid. Among these, recent genetic and pathological evidence with large data strongly supported the third hypothesis: the amyloid hypothesis. This hypothesis emphasizes that the increasing of amyloid beta (Aβ) peptide leads to an extracellular accumulation of Aβ in the brain resulting in the formation of inflammatory amyloid plaques. This can lead to lesion of synapses, nerve fiber entanglements, and reduction in the number of neurons.

In this dissertation, we studied the influence of mutants and sequence Aβ41 on structures and dynamics of Aβ40 and Aβ42. Aβ41 sequence was chosen to elucidate the differences in aggregation pathway of Aβ40 and Aβ42. Our study on properties of Aβ41showed that the last hydrophobic residue Ala42 has a strong impact to the increased fibril formation rate and consequently neurotoxicity of Aβ peptides. Another experimental investigation showed that triple mutation G33V-V36P-G38V (VPV) alters Aβ42-WT to the "*super*–Aβ42" formation and changes the oligomerization pathways of Aβ40-VPV similar to Aβ42-WT. By simulating both segments ($A\beta_{31\text{-}40}$, $A\beta_{31\text{-}42}$) and full

length ($A\beta_{1-40}$, $A\beta_{1-42}$), we conclude that the similarity in folding pathway of Aβ40-VPV and Aβ42-WT was not only caused by the enhancement of β-turn structure but also by the increase of β-content in the whole sequence under mutation. The structural changes of Aβ42 under VPV mutation are based on the enhancement on β-hairpin and β-turn at residue 36-37 at C-terminal. The Glycine zipper motif at the C-terminus remarkably affected the aggregation rate and formation toxicity of the Aβ peptide. To validate the influence of Glycine zipper on Aβ42 properties, we destabilized the Glycine zipper structure by substituting Glycine with Valine at residue 37 and characterized the biochemical properties along with structures of Aβ42 (G37V) by simulation and invitro experiment. G37V mutation was found to strongly reduce the toxicity but did not increase the aggregation rate nor altering the secondary structures. In addition, the aggregation morphology of Aβ42 (G37V) has an ellipse-like aggregate while it is a network-like fibril in Aβ42. One of the possible cause that related to the reduction of toxicity is the different aggregation morphology. The simulation result showed that G37V mutation did not change the secondary structure but rather caused an increase the β-turn and β-hairpin content at the C-terminus. Furthermore, the Asp23-Lys28 salt bridge of G37V was more flexible than that of the wildtype. These unique structural features contributed to the possible reason to explain for the ellipse-like morphology.

Previous studies have shown that the environmental factors (pH, temperature, salt concentration, etc.) and the intrinsic structures of protein (hydrophobicity, charge, fibril prone in monomeric state, fibril mechanical stability) control the aggregation rate of the protein. Experimental studies showed that the fibril structures consist of cross β-sheets. Thus, sequences that have a high β content in the monomeric state should have high aggregation rates and study the structure of the monomer can help inferring fibril growth process. Nevertheless, this hypothesis has not been proven until now. We used the experimental aggregation rates κ from previous studies and do simulation for Aβ42 wild type and its 19 mutations to find the β-content in monomer state. The high correlation factor of the relation between κ and β conclude that the beta content in the monomeric

state control the aggregation rate of amyloid β. From our result, we have answered an important question about the dependence of aggregation rate of the monomeric β-structure on a quantitative level. The equation between the aggregation rate and β-content gave us a tool to estimate the aggregation rate using the β-content, which can be easily obtained by REMD simulation.

The main scientific contributions

This dissertation has the main scientific contributions as follows:

- In the two last residues of Aβ42, Ala42 is the main reason in decision the difference aggregation rate and toxicity of Aβ42 compare to Aβ40.
- Triple point mutation G33V-V36P-G38V makes Aβ40 has oligomerization pathway similar to those of Aβ42 wild type and Aβ42 become super-Aβ42 with elevated aggregation rates and toxicity.
- G37V mutation destroys the Glycine zipper motif at C-terminus of Aβ42, changes the aggregation morphology by forming an ellipse-shape like aggregates instead of network-like fibril like Aβ42 wild type and also reduce the toxicity.
- Our result have shown explicity that the experiment measured aggregation rate κ is controlled by the calculated β-content in monomeric state. Based on the equation expressed by exponential and linear fit between κ and β in such a way that the higher the β-propensity the faster formation of fibril, we can estimate the aggregation rate through calculation the β-content.

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