Conformational Stability of Non-Fibrillar Amyloid-β_{17-38} – A Molecular Dynamics Study

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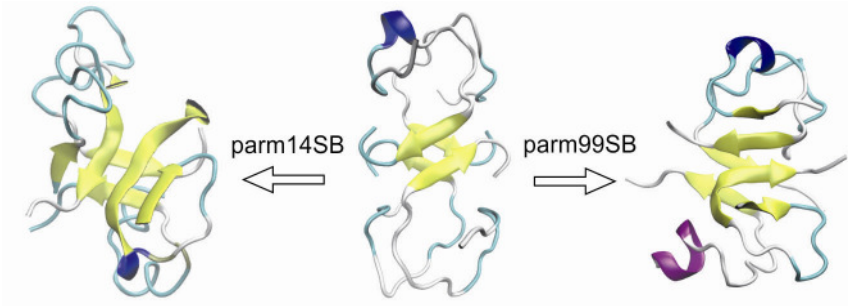
Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder in industrial nations. Patients suffering from AD develop senile plaque deposits in their brains, which mainly consist of fibrillary aggregates of amyloid β (Aβ) peptides. Recent findings, however, suggest that neurotoxicity is conferred by small soluble Aβ oligomers instead of unsoluble Aβ fibrils. Unfortunately, Aβ peptides exhibit a vast conformational variety and plethora of oligomeric states, which has been making experimental studies of their structure a major challenge.

In 2011, Streltsov et al. succeeded in capturing a non-fibrillar tetramer structure of $A\beta_{18-41}$ with its sequence fused into a loop region of a shark Ig new antigen receptor.[1] Recently, we investigated the stability of this isolated Aβ tetramer structure in dependence of the C-terminal length and found, that the longer species $A\beta_{17-42}$ and $A\beta_{17-43}$ were conformationally stable already at the level of the monomer, whereas $A\beta_{17-40}$ completely lost the initial fold.[2]

Here, we present complementing molecular dynamics simulations of the C-terminally further truncated species $A\beta_{17-38}$. The isoform $A\beta_{38}$ is found in plaque deposits as well as in cerebrospinal fluid and blood [3] and exhibits different neuronal properties in mixtures: while it shows neuroprotective effects upon the longer species $A\beta_{42/43}$, it increases the neurotoxicity of $A\beta_{40}$. This work aimed at elucidating the $A\beta_{38}$ tetramer dynamics in relation to the other Aβ species.[4]

Like in our previous work, the structure 3MOQ [1] served as template for the generation of $A\beta_{17-38}$ tetramer as well as derived dimer and monomer structures. The systems were simulated with AMBER14 in two runs using two different force fields (parm99SB, parm14SB) in explicit water.



All monomer structures of $A\beta_{17-38}$ quickly lost their initial conformation and unfolded displaying a pronounced flexibility. The two kinds of $A\beta_{17-38}$ dimers showed slight differences in their dynamics, but were not conformationally stable as well. Surprisingly, the tetramer kept the characteristics of the starting structure, independent of the force field used: the interfaces between the peptide chains were stabilized by an antiparallel β-sheet and hydrophobic contacts within the core of the tetramer. These dynamical properties of $A\beta_{38}$ are in accord with the notion that the distinct molecular plasticity of different Aβ species regulates their oligomerization and cytotoxicity.[4]

[1] V. A. Streltsov, J. N. Varghese, C. L. Masters, S. D. Nuttall, *J. Neurosci.*, **2011**, *31*, 1419-1426.
[2] E. Socher, H. Sticht, A. H. C. Horn, *ACS Chem. Neurosci.*, **2014**, *19*, 161-167.
[3] J. Wiltfang, H. Esselmann, M. Bibl, A. Smirnov, M. Otto, S. Paul, B. Schmidt, H.-W. Klafki, M. Maler, T. Dyrks, M. Bienert, M. Beyermann, E. Rüther, J. Kornhuber *J. Neurochem.* **2002**, *81*, 481-496.
[4] A. Vandersteen, M. F. Masman, G. de Baets, W. Jonckheere, K. van der Werf, S. J. Marrink, J. Rozenski, I. Benilova, B. de Strooper, V. Subramaniam, J. Schymkowitz, F. Rousseau, K. Broersen, *J. Biol. Chem.* **2012**, *287*, 36732-36743.