

What Does the Prion Amyloid Fibril Structure in AGAAAAGA Look Like?

Jiapu Zhang*

School of Science, Informatics Technology and Engineering and Centre of Informatics and Applied Optimisation, The Federation University of Australia, MT Helen Campus, Victoria 3353, Australia

Keywords: Prion amyloid fibril; Molecular structure; AGAAAAGA segment

Protein misfolding into structures such as amyloids is a key feature of many disorders of humans. Neurodegenerative diseases, including more than 20 kinds of Parkinson's disease, Alzheimer's disease ($\text{A}\beta$), Huntington's disease, Parkinson's disease, Prions' diseases, β -Secretase, etc, are protein misfolding diseases. Neurodegenerative diseases are also called conformational diseases in that a functional native or mutant protein undergoing a conformational transition will lead to protein aggregation or formation of amyloid fibrils. This conformational transition may be attempted to study by MD (Molecular Dynamics) techniques. We also use QM/MM (Quantum Mechanics / Molecular Mechanics) approaches (a small active site / substrate region is treated with QM with the rest of the system treated with classical MM) to predict the structure and relative stability of mutant proteins associated with neurodegenerative diseases. Neuro-degenerative diseased amyloid fibrils are unstable, non-crystalline and insoluble so that their structures are very difficult to be determined in laboratory by experimental X-ray crystallography, NMR (Nuclear Magnetic Resonance) spectroscopy, dual polarization interferometry. MM (Molecular Modeling) skills such as mathematical optimization can allow us to construct many amyloid fibril models for neurodegenerative diseases and unstructured regions of proteins. This is to say MD, QM/MM, MM computing can allow us to study protein misfolding neurodegenerative diseases with the amyloid fibril structures. Particularly, this paper will study the PrP (113-120) region (AGAAAAGA) of prion diseases to get its MD and MM computational molecular structures. Because there is little X-ray or NMR structural data available to date on AGAAAAGA, the studies of this paper may be useful for the goals of medicinal chemistry.

Firstly, in computational theory, by the fibril prediction program [1] we can identify that prion AGAAAAGA (PrP (113-120)) owns the amyloid fibril formation property (Figure 1).

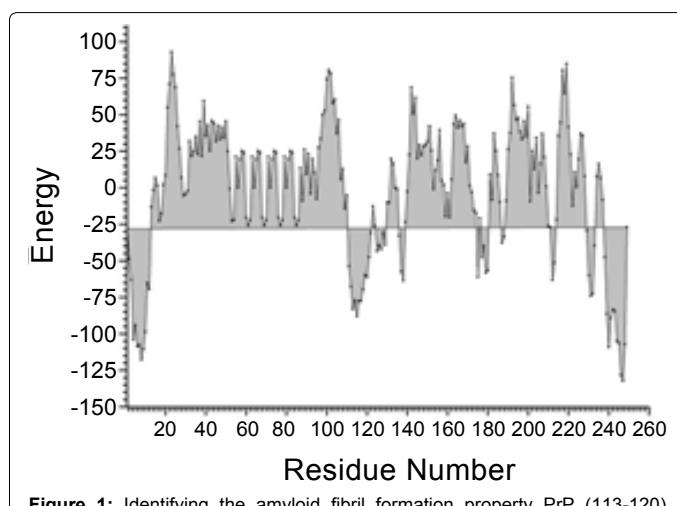


Figure 1: Identifying the amyloid fibril formation property PrP (113-120) AGAAAAGA region is identified to own the amyloid fibril formation property.

Secondly, in laboratory works, the prion AGAAAAGA region has also been identified to own the amyloid fibril formation property [2-21].

Thirdly, we answer the question "What does the prion amyloid fibril structure in AGAAAAGA look like?" Gasset et al. [20] reported there are similarities between the PrP sequence AGAAAAGA and that of silkworm fibroin, and the homology between PrP sequence AGAAAAGAVVGLGG and that of spider fibroin. Thus, we may say that the hydrophobic region of PrP (109-136) should be a region to form β -sheets and amyloid polymers, instead of α -helices of the Garnier-Robson analysis [22]. Our MD and MM (where the β -sheet structure is maintained by van der Waals hydrophobic contacts and hydrogen bond interactions in 3-dimensional protein structures, which can be represented as mathematical optimization problems of Lennard-Jones potential energy and hydrogen bond potential energy) computations show that prion AGAAAAGA amyloid fibrils should have the Class 7 (β -strand antiparallel, face=back, up-up) and Class 1 (β -strand parallel, face-to-face, up-up) structure of [7,23,4,15].

In conclusion, this paper solves a problem on the amyloid fibril structures of prion AGAAAAGA region; it has an amyloid fibril β -sheet structure Class 1 or 7. This shows that MD, QM/MM, MM computations play a very important role to reveal the protein misfolding conformational diseases.

References

1. Zhang Z, Chen H, Lai L (2007) Identification of amyloid fibril-forming segments based on structure and residue-based statistical potential. *Bioinformatics* 23: 2218-2225.
2. Brown DR (2000) Prion protein peptides: optimal toxicity and peptide blockade of toxicity. *Mol Cell Neurosci* 15: 66-78.
3. Hölscher C, Delius H, Bürkle A (1998) Overexpression of nonconvertible PrP δ delta114-121 in scrapie-infected mouse neuroblastoma cells leads to trans-dominant inhibition of wild-type PrP(Sc) accumulation. *J Virol* 72: 1153-1159.
4. Cheng HM, Tsai TW, Huang WY, Lee HK, Lian HY, et al. (2011) Steric zipper formed by hydrophobic peptide fragment of Syrian hamster prion protein. *Biochemistry* 50: 6815-6823.
5. Lee SW, Mou Y, Lin SY, Chou FC, Tseng WH, et al. (2008) Steric zipper of the amyloid fibrils formed by residues 109-122 of the Syrian hamster prion protein. *J Mol Biol* 378: 1142-1154.

*Corresponding author: Jiapu Zhang, School of Science, Informatics Technology and Engineering and Centre of Informatics and Applied Optimisation, The Federation University of Australia, MT Helen Campus, Victoria 3353, Australia, Tel: 61-423487360, 61-3-5327 6335; E-mail: jiapu_zhang@hotmail.com; j.zhang@federation.edu.au

Received March 20, 2014; Accepted March 21, 2014; Published March 31, 2014

Citation: Zhang J (2014) What Does the Prion Amyloid Fibril Structure in AGAAAAGA Look Like?. *Biochem Pharmacol* 3: e158. doi:10.4172/2167-0501.1000e158

Copyright: © 2014 Zhang J. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

6. Jones EM, Wu B, Surewicz K, Nadaud PS, Helmus JJ, et al. (2011) Structural polymorphism in amyloids: new insights from studies with Y145Stop prion protein fibrils. *J Biol Chem* 286: 42777-42784.
7. Sawaya MR, Sambashivan S, Nelson R, Ivanova MI, Sievers SA, et al. (2007) Atomic structures of amyloid cross-beta spines reveal varied steric zippers. *Nature* 447: 453-457.
8. Kajava AV, Squire JM, Parry DA (2006) Beta-structures in fibrous proteins. *Adv Protein Chem* 73: 1-15.
9. Wagoner VA, Cheon M, Chang I, Hall CK (2011) Computer simulation study of amyloid fibril formation by palindromic sequences in prion peptides. *Proteins* 79: 2132-2145.
10. Sasaki K, Gaikwad J, Hashiguchi S, Kubota T, Sugimura K, et al. (2008) Reversible monomer-oligomer transition in human prion protein. *Prion* 2: 118-122.
11. Haigh CL, Edwards K, Brown DR (2005) Copper binding is the governing determinant of prion protein turnover. *Mol Cell Neurosci* 30: 186-196.
12. Kourie JI, Kenna BL, Tew D, Jobling MF, Curtain CC, et al. (2003) Copper modulation of ion channels of PrP[106-126] mutant prion peptide fragments. *J Membr Biol* 193: 35-45.
13. Norstrom EM, Mastrianni JA (2005) The AGAAAAGA palindrome in PrP is required to generate a productive PrPSc-PrPC complex that leads to prion propagation. *J Biol Chem* 280: 27236-27243.
14. Zanuy D, Ma B, Nussinov R (2003) Short peptide amyloid organization: stabilities and conformations of the islet amyloid peptide NFGAIL. *Biophys J* 84: 1884-1894.
15. Ma B, Nussinov R (2002) Molecular dynamics simulations of alanine rich beta-sheet oligomers: Insight into amyloid formation. *Protein Sci* 11: 2335-2350.
16. Wegner C, Römer A, Schmalzbauer R, Lorenz H, Windl O, et al. (2002) Mutant prion protein acquires resistance to protease in mouse neuroblastoma cells. *J Gen Virol* 83: 1237-1245.
17. Kourie JI (2001) Mechanisms of prion-induced modifications in membrane transport properties: implications for signal transduction and neurotoxicity. *Chem Biol Interact* 138: 1-26.
18. Jobling MF, Stewart LR, White AR, McLean C, Friedhuber A, et al. (1999) The hydrophobic core sequence modulates the neurotoxic and secondary structure properties of the prion peptide 106-126. *J Neurochem* 73: 1557-1565.
19. Chabry J, Caughey B, Chesebro B (1998) Specific inhibition of in vitro formation of protease-resistant prion protein by synthetic peptides. *J Biol Chem* 273: 13203-13207.
20. Gasset M, Baldwin MA, Lloyd DH, Gabriel JM, Holtzman DM, et al. (1992) Predicted alpha-helical regions of the prion protein when synthesized as peptides form amyloid. *Proc Natl Acad Sci U S A* 89: 10940-10944.
21. Govaerts C, Wille H, Prusiner SB, Cohen FE (2004) Evidence for assembly of prions with left-handed beta-helices into trimers. *Proc Natl Acad Sci U S A* 101: 8342-8347.
22. Garnier J, Osguthorpe DJ, Robson B (1978) Analysis of the accuracy and implications of simple methods for predicting the secondary structure of globular proteins. *J Mol Biol* 120: 97-120.
23. Zhang J, Zhang Y (2013) Molecular dynamics studies on 3D structures of the hydrophobic region PrP(109-136). *Acta Biochim Biophys Sin (Shanghai)* 45: 509-519.