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Molecular Dynamics of Amylin Amyloid Single Beta-Sheet

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Abstract. **Amyloidosis are metabolic conformational diseases caused by misfolding and aggregation of soluble proteins in insoluble fibrils which deposit squeezing out the functioning cells or block cell-to-cell connectivity. Amylin or Islet Amyloid Polypeptide (IAPP) is a 37 residue peptide hormone secreted by pancreatic β-cells together with insulin. Amylin forms deposits in pancreas and is a non-insulin-dependent type II diabetes disease agent. Six stranded single ß-sheets of amylin 10-29 residues QRLANFLVHSSNNFGAILSS (Amylin 10-29), was investigated by molecular dynamics (MD) simulations in a periodic box using Amber 9.0, f99 force field and isothermal-isobaric ensemble, NTP protocol (constant temperature, pressure and the number of particles). The total MD run was 193 ns for Amylin 10-29.**

MD simulations show that a) Amylin 10-29 ß-sheet is bound together mainly by backbone hydrogen bonding, b) The ß-sheet is stabilized by side chain hydrogen bonding between asparagine residues and between residues Ser^{20} and Asp^{22} c). The ß-strands of Amylin 10-29 are glued together by leucine, isoleucine, valine residues and by phenylalanine residues, which together with asparagine residues form a sub-stack kept together by mild polar interactions, d) The C terminal part of the Amylin 10-29 ß-sheet has the hydrophobic anchor of isoleucine and leucine residues Ile^{26}-Leu^{27} which could be used to bind nearby ß-sheets in the ß-sheet protofibril. This binding should stabilize the ß-structure of a separate ß-sheet. e). In the Amylin 10-29 region Ser^{19}-Ser^{20}-Asn^{21}-Asn^{22} the ß-sheet has the W-shaped bend with the deeper vertex on Ser^{20} and smaller vertex on Asn^{22}, suggesting that also the bent ß-sheet could be possible.

Keywords: **Amylin, amyloidosis, molecular dynamics, beta-sheet.**

I. Introduction

Amyloidoses are metabolic conformational diseases caused by misfolding and aggregation of soluble proteins in insoluble fibrils which replace the functioning cells or block cell-to-cell connectivity. Amyloid deposits or oligomeric preamyloid aggregates of specific amyloid fibril proteins, are important in the pathogenesis of about 30 diseases by exerting toxic effects on cells [1]. Amyloid fibrils cause such diseases as Alzheimer's disease (caused by Amyloid-β-protein) [2, 3], chronic inflammation Amyloidosis (caused by serum amyloid protein), type II diabetes (caused by Islet amyloid protein), Parkinson's disease (caused by α-synuclein) [4], dialysis related amylodosis (caused by β-2–microglobulin), Hungtington disease (due to mutations and subsequent aggregation of protein hungtingtin), spongiform encephalopaties - Creutzfeld-Jacob disease (caused by prion protein [5])), amyotrophic lateral sclerosis [6], Finnish familial amyloidoses (caused by gelsolin mutation), medullary carcinoma of thyroid (caused by calcitonin) .

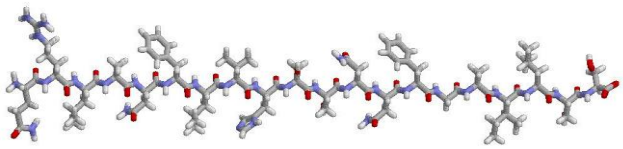

Fig.1. **Amylin 10-29,** QRLANFLVHSSNNFGAILSS

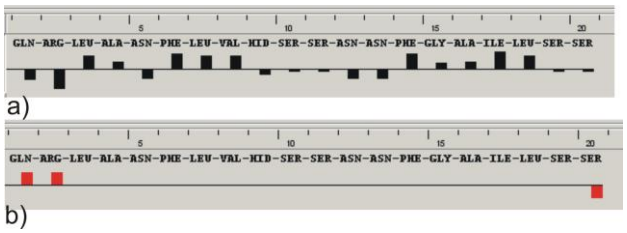

Fig.2. a) Hydrophobicity and b) charge properties of Amylin 10-29 (above the line – positive, down the line – negative) (calculated by program MOE [22]).

Amyloids are mainly composed of β-sheet structure in which the polypeptide chains are held together by hydrogen bonding. These hydrogen bonding interactions are probably characteristic of all amyloid fibrils. Amyloid cross-β-structure is a stable structure, in which protein or peptide chains are glued together by hydrogen bonding and hydrophobic interactions, β-strands are placed orthogonaly to the fiber axis, and the backbone hydrogen bonding run parallel to the fiber axes. It is postulated that the cross- β-structure is an energetic minimum for aggregated proteins or peptides and its formation is an intrinsic property of proteins or peptides [7]. Amyloid fibrils can be also formed by polypeptides which are not involved in any known amyloid disease.

It remains unclear why amyloidogenic proteins form oligomers *in vivo*, what is the exact structure of the oligomers, and what is their cytotoxic role in human disorders [8].

Amylin or Islet Amyloid Polypeptide (IAPP) is a 37 residue peptide endocrine hormone coexpressed and cosecreted with insulin by pancreatic β-cells. The physiological function of IAPP is unknown [8], but it is known that amylin inhibits insulin-mediated glucose uptake [8] and action of amylin effect on β-cells is to inhibit insulin secretion [9], amylin delays gastric emptying and suppresses appetite [10], although

it is unclear whether these actions are physiological actions of IAPP within normal circulating levels [8].

Amylin forms deposits in pancreas and is a non-insulin-dependent type II diabetes disease agent [2]. The more amylin amyloid plaques, the severer is type II diabetes. Amylin builds 90% of the amyloid deposits found in type II diabetic patients [11]. Aggregates of amylin are toxic and may be responsible for β-cell death as type 2 diabetes progresses [8, 12-13].

In this work we studied the mechanism of the formation of amiloid fibrils from amylin by means of molecular dynamics (MD) with the Amber 9.0, f99 force [14-15] field. We considered a six-stranded parallel single ß-sheet of amylin 10-29 (**Amylin 10-29**) (Fig.1-Fig. 2)

Gln^{10}-Arg^{11}-Leu^{12}-Ala^{13}-Asn^{14}-Phe^{15}-Leu^{16}-Val^{17}-His^{18}-Ser^{19}-Ser^{20}-Asn^{21}-Asn^{22}-Phe^{23}-Gly^{24}-Ala^{25}-Ile^{26}-Leu^{27}-Ser^{28}-Ser^{29}

for which we ran a 193 ns simulation.

II. Methods

The six stranded parallel, flat Amylin 10-29 ß-sheet was surrounded by chlorine counter ions to neutralize the charge and placed in a periodic water box of explicit water molecules with 5 Å layer over the solute. The system consisting of 8856 atoms was minimized and subjected to molecular dynamics (MD) by Amber 9.0 program package [14-16], f99 force field, NTP protocol (constant number of particles, temperature, pressure). The system temperature was risen stepwise from T=10K till T=309 K in 45.1 ns of the MD run, then the systems were simulated at the constant temperature of 309 K. The total MD run for Amyl 10-29 was 193 ns.

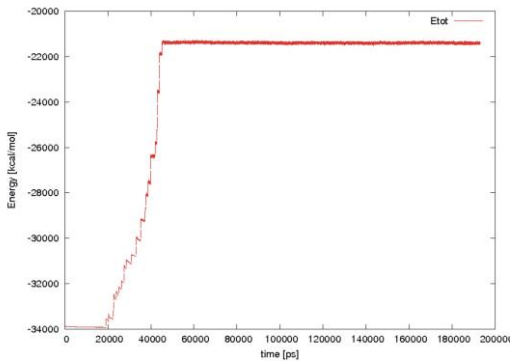

Fig. 3. Energy of Amylin 10-29 ß-sheet MD run.

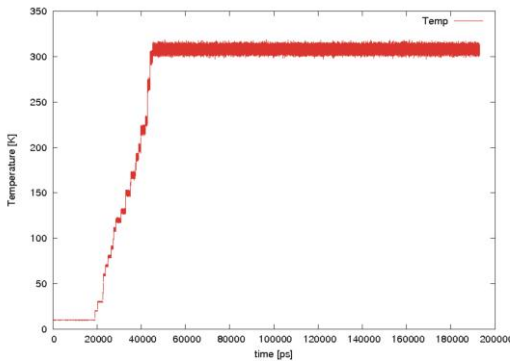

Fig. 4. Temperature of Amylin 10-29 MD run.

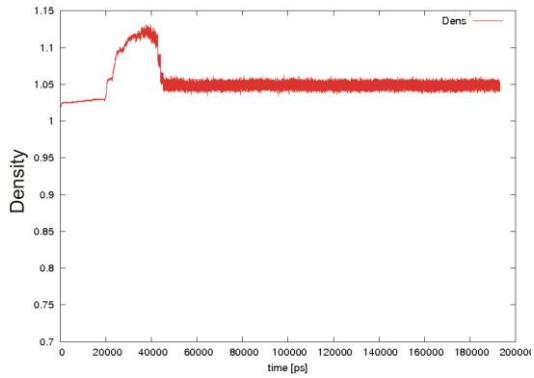

Fig.5. Density of Amylin 10-29 system in the course of MD run.

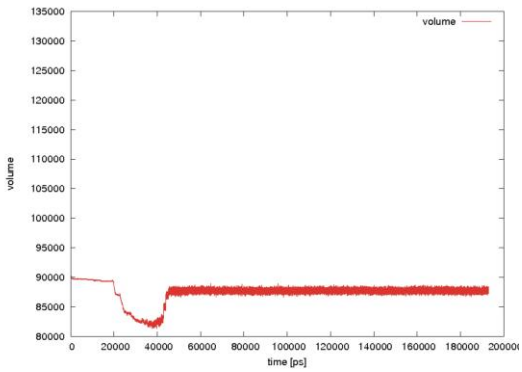

Fig.6. Volume of Amylin 10-29 system in the course of MD run

III. Results and Discussion

The system energy was stable and temperature, density and volume were constant after 45,2 ns of MD run (Fig.3-Fig.6).

The single ß-sheet of Amylin 10-29 exhibits stable ß-sheet structure during the course of MD run for 193 ns. ß-sheet stretches across the N-terminal regions Arg^{11}-Val^{17} and time to time expands till Ser^{19}, besides two strands have stable ß-sheet over the region Asp^{22}-Leu^{27}. In the Amylin 10-29 region Ser^{19}-Ser^{20}-Asn^{21}-Asn^{22} the ß-sheet has the W-shaped bend with the deeper vertex on Ser^{20} and smaller vertex on Asn^{22}, suggesting that also the bent ß-sheet could be possible (Fig. 13 - Fig. 14, Fig. 16 - Fig. 17). The turn region detected by MD is in accordance with the experimental data of NMR on the whole amylin 1-37 in detergent micelles as the membrane-mimicking environment, denoting that the α-helix of amylin has a kink or discontinuity near residues 18–22 [17, 18] and noting that in the micelle-bound states of amyloidogenic proteins, kinks or distortions from α-helix conformations correlate with the locations of turns in the fibrillar β-sheet structures [19].

Also M. Apostolidou investigating amylin on the micellae surfaces stresses that residues Asn^{21} and Asn^{22} are located in a transitional region between the α-helical structure and C-terminus and exhibit significant mobility [20]. The higher mobility and flexibility of C-terminal part of the Amylin 10-29 ß-sheet was observed also in the present study.

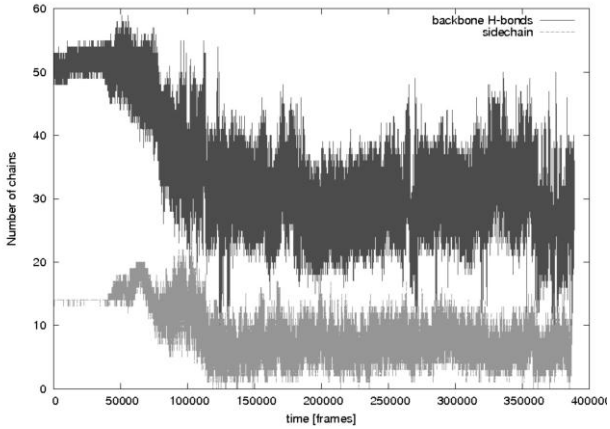

Fig.7. Hydrogen bonding of of Amylin 10-29 ß-sheet. Number of backbone hydrogen bonds –black, number of sidechain hydrogen bonds – gray. The system is kept together mainly by backbone hydrogen-bonding, and the sidechain hydrogen bonds stabilize the system.

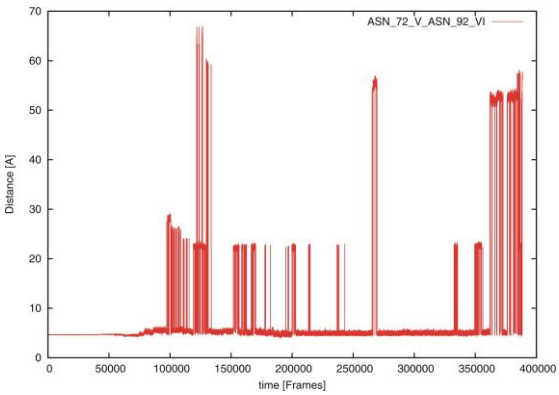

Fig.10. Mass center distances between Asn21 (V strand)-Asn21 (VI strand)

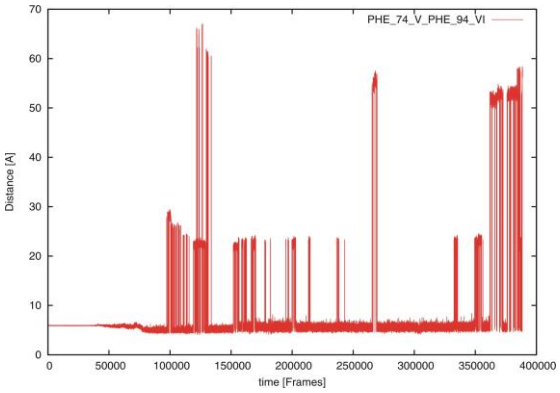

Fig.8 Mass center distances between Phe23 (V strand)-Phe23 (VI strand)

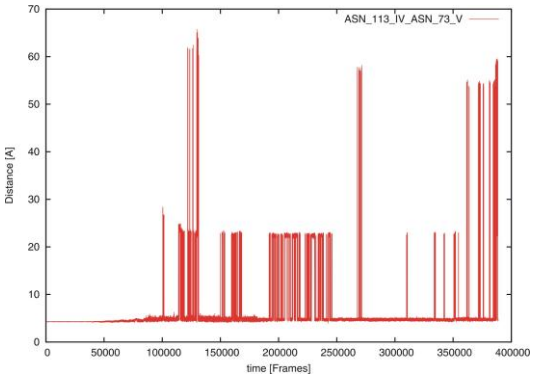

Fig.11. Mass center distances between Asn22 (IV strand) - Asn22 (V strand)

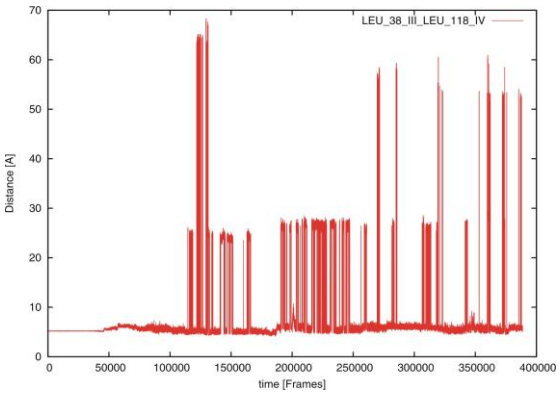

Fig.9. Mass center distances between Leu 27 (III strand)-Leu27 (IV strand)

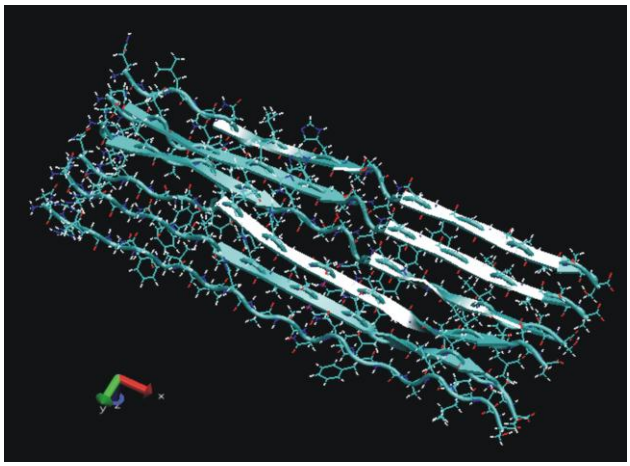

Fig.12. Amylin 10-129 29 ß-sheet after 1 ns of MD run – front view.

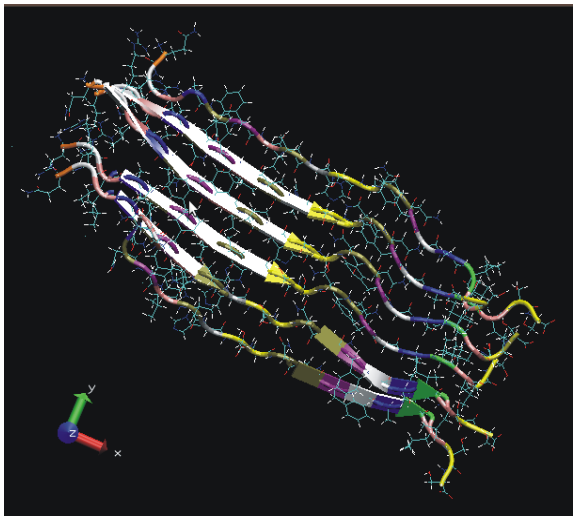

Fig.13. Amylin 10-29 29 ß-sheet after 4.5 ns of MD run - front view.

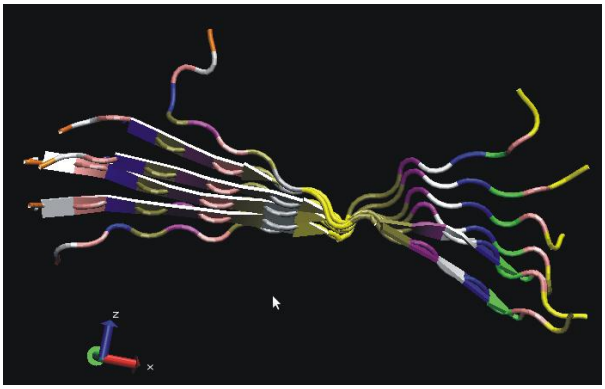

Fig.16. Amylin 10-29 ß-sheet after 4.5 ns of MD run. – sideview. In the region Ser^{19}-Ser^{20}-Asn^{21}-Asn^{22} the ß-sheet has W-shaped bend with the deeper vertex on Ser^{20} and smaller vertex on Asn^{22}.

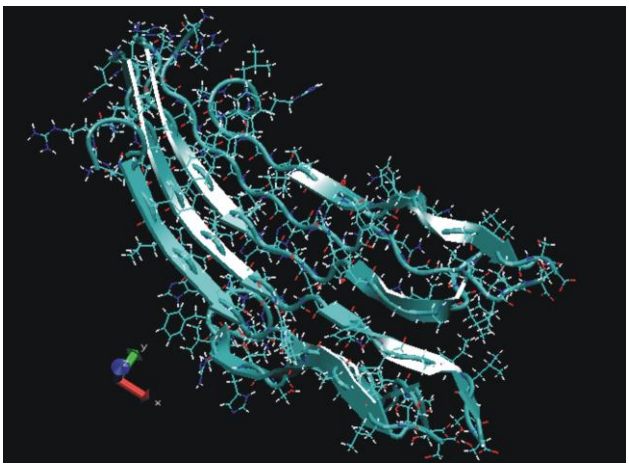

Fig.14. Amylin 10-29 29 ß-sheet after 193 ns of MD run – front view.

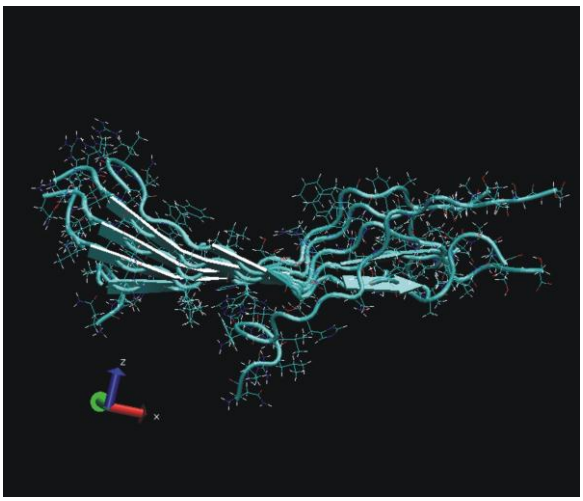

Fig.17. Amylin 10-29 ß-sheet after 190 ns of MD run. – sideview. The single Amylin 10-29 strand (in front) which separated from the ß-sheet loses its ß-structure and turns to coil-coil conformation, so that in appropriate conditions could turn to α-helix

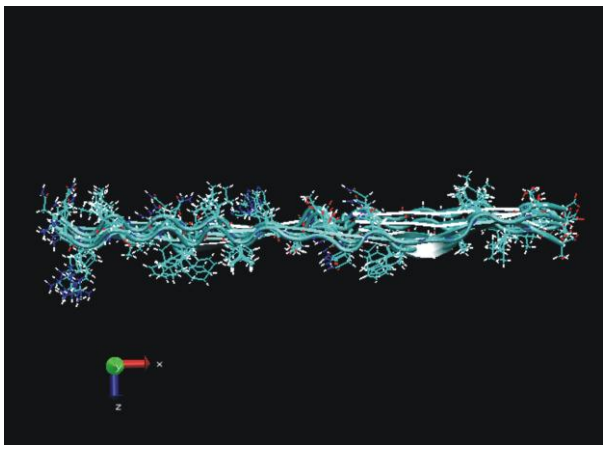

Fig.15. Amylin 10-29, started from a parallel, flat ß-sheet after 1 ns of MD run – sideview.

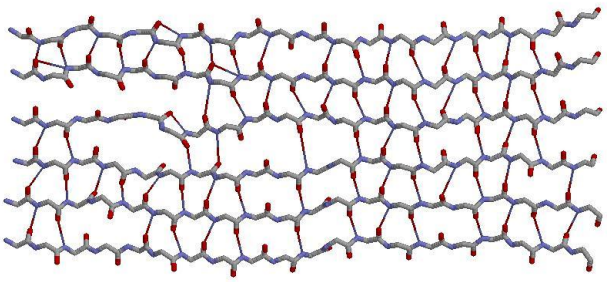

Fig.18. Hydrogen bonding of Amylin 10-29 ß-sheet backbones after 1 ns of MD run

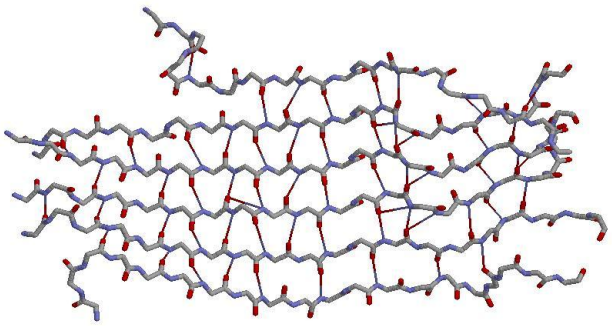

Fig.19. Hydrogen bonding of Amylin 10-29 ß-sheet backbones after 80 ns of MD run. The few H-bonds perpendicular to valence bonds are artifact of RASMOL image.

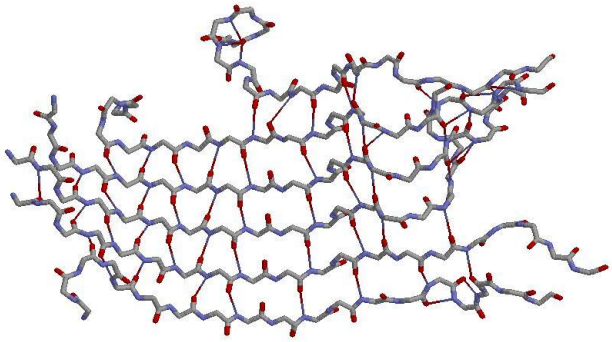

Fig.20. Hydrogen bonding of Amylin 10-29 ß-sheet backbones after 193 ns of MD run. The few H-bonds perpendicular to valence bonds are artifact of RASMOL image

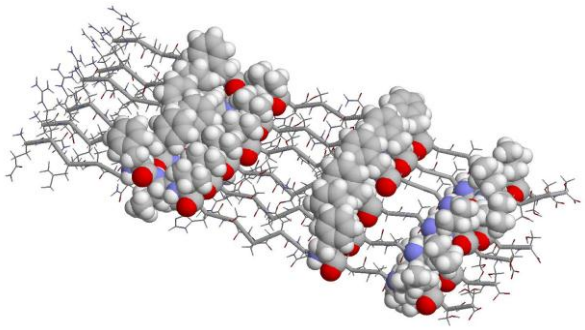

Fig.21. Hydrophobic cores made by Phe^{15}-Leu^{16}-Val^{17}, Phe^{23} and Ile^{26}-Leu^{27} after 1 ns of MD run.

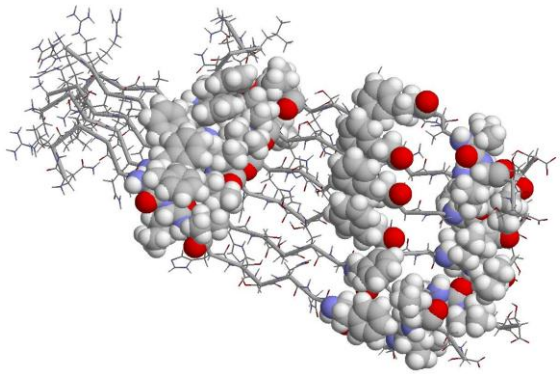

Fig. 22. Hydrophobic cores made by Phe^{15}-Leu^{16}-Val^{17}, Phe^{23} and Ile^{26}-Leu^{27} after 80 ns of MD run.

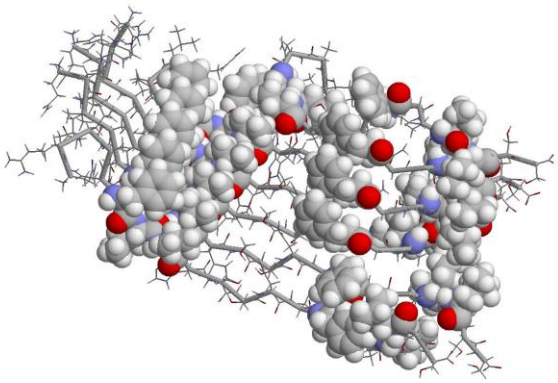

Fig.23. Hydrophobic cores made by Phe^{15}-Leu^{16}-Val^{17}, Phe^{23} and Ile^{26}-Leu^{27} after 80 ns of MD run.

Amylin 10-29 ß-sheet is stabilized mainly by interstrand backbone hydrogen bonding (Fig. 7, Fig. 18 - Fig.20). Apart from backbone hydrogen bonding the ß-sheets of Amylin 10-29 are stabilized by side chain hydrogen bonding between asparagine residues and between residues Ser^{20} and Asp^{22}. Most of the hydrogen bonding interactions are localized within the N-terminal of the Amylin 10-29 ß-sheet and in the middle of the ß-sheet. There are some flickering salt-bridges between Arg^{11} and the backbone carbonyl of the neighboring strand, and flickering hydrogen bonds between Ser^{28} and Ser^{29} of the neighboring strands.

The hydrophobic interactions also play important role in formation of Amylin 10-29 ß-sheet: the ß-strands of Amylin 10-29 are glued together by leucine, isoleucine, valine residues and by phenylalanine residues, which together with asparagine residues form a sub-stack kept together by mild polar interactions. The C terminal part ß-sheet has a strong hydrophobic anchor formed by Ile^{26}-Leu^{27} which might be used to bind nearby ß-sheets in the ß-sheet stack. This binding could stabilize the ß-structure of a separate ß-sheet in the protofibril.

The stability of the Amylin 10-29 ß-sheet is confirmed by constant distances between mass centers of the neighboring residues (Fig 8 - Fig. 11). The peaks are due to jumping of some strand in the neighboring periodic box.

The single Amylin 10-29 strand which separates from the ß-sheet loses its ß-structure and turns into coil-coil conformation, so that in appropriate conditions could turn to α-helix (Fig. 17).

During the course of our simulation the turn of the ß-sheet stays on the region Ser^{19}-Ser^{20}-Asn^{21}-Asn^{22}. Mascioni [18], measuring a shorter fragment of amylin 20-29 described the turn center on Phe23, Gly24, but it could be connected with free N-terminal end of Ser^{20}. In Amylin 10-29 the turn might comprise a wider region (Ser19-Gly24), and the exact place of the turn depending on surrounding residues.

IV. Conclusions

1. Amylin 10-29 ß-sheet N-terminal part is more stable than the C-terminal part. The N-terminal part of the Amylin 10-

29 ß-sheet has ß-structure over the region Arg^{11}-Val^{17}, and fluctuating ß-structure over the region Val^{17} - Ser^{19}.

2. Amylin 10-29 ß-sheet C- terminal part comprises Asp^{22}-Leu^{27}. The C terminal part ß-sheet has the hydrophobic anchor Ile^{26}-Leu^{27} which might be used to bind nearby ß-sheets. This binding could stabilize the ß-structure of a separate ß-sheet.
3. In the Amylin 10-29 region Ser^{19}-Ser^{20}-Asn^{21}-Asn^{22} the ß-sheet has a W-shaped bend with the deeper vertex on Ser^{20} and smaller vertex on Asn^{22}, suggesting that also the bent ß-sheet could be possible.
4. Amylin 10-29 ß-sheet is bound together mainly by backbone hydrogen bonding. The ß-sheet is stabilized by side chain hydrogen bonding between asparagine residues and between residues Ser^{20} and Asp^{22}.
5. The ß-strands of Amyl 10-29 are bound together by leucine, isoleucine, valine residues and by phenylalanineresidues, which together with asparagine residues form a sub-stack kept together by mild polar interactions.
6. The single ß-sheet side chain positions suggest that hydrophobic interactions of leucine and isoleucine residues could keep together the ß-sheet stack in Amylin 10-29 protofibrils.

ACKNOWLEDGMENTS

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REFERENCES

1. **Westermark, P.** Aspects on human amyloid forms and their fibril polypeptides. FEBS Journal, 2005, v. 272, p. 5942–5949.
2. **Hardy, J., Selkoe, D.J.** The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science, 2002, v. 297, p.:353–356.
3. **Tanzi R.E, Bertram, L.** Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. Cell, 2005, v.120, p.545–555.
4. **Ryu, E.J., Harding, H.P., Angelastro, J.M,, Vitolo, O.V,, Ron, D,, Greene, L.A.** Endoplasmic reticulum stress and the unfolded protein response in cellular models of Parkinson's disease. J Neurosci, 2002, v. 22, p. 10690–10698.
5. **Simoneau, S., Rezaei, H,, Sales, N., Kaiser-Schulz, G., Lefebvre-Roque, M., Vidal, C., Fournier, J.G., Comte, J., Wopfner, F., Grosclaude, J., Schatzl, H, Lasmezas, C.I.** In vitro and in vivo neurotoxicity of prion protein oligomers. PLoS Pathog ., 2007, 3, e125.
6. **Wootz, H., Hansson, I., Korhonen, L., Napankangas, U., Lindholm, D.** Caspase-12 cleavage and increased oxidative stress during motoneuron degeneration in transgenic mouse model of ALS. Biochem. Biophys. Res. Commun., 2004, v. 322, p 281–286.
7. **Dobson, C. M.** Protein folding and misfolding. Nature, 2003, v. 426, p. 884–890.
8. **Haataja, L., Gurlo, T., Huang, C.J.,Butler, P.C.** Islet Amyloid in Type 2 Diabetes, and the Toxic Oligomer Hypothesis. Endocrine Reviews, 2008, v. 29, p.303-316.
9. **Ohsawa, H, Kanatsuka, A., Yamaguchi, T., Makino, H, Yoshida, S.** Islet amyloid polypeptide inhibits glucose-stimulated insulin secretion from isolated rat pancreatic islets. Biochem. Biophys. Res. Commun., 1989, v. 160, p.961–967.
10. **Rivera, E., Straub, J., Thirumalai, D**. Sequence and Crowding Effects in the Aggregation of a 10-Residue Fragment Derived from Islet Amyloid Polypeptide. Biophysical Journal, 2009, v. 96, p. 4552–4560.
11. **Arnelo, U., Permert, J., Larsson, J., Reidelberger, R.D., Arnelo, C., Adrian, T.E.** Chronic low dose islet amyloid polypeptide infusion reduces food intake, but does not influence glucose metabolism, in unrestrained conscious rats: studies using a novel aortic catheterization technique. Endocrinology, 1997, v.138, 4081–4085.
12. **Janson, J., Ashley, R. H., Harrison, D., McIntyre, S., Butler, P. C.** The mechanism of islet amyloid is membrane disruption by intermediate-sized toxic amyloid particles. Diabetes, 1999, v. 48, p 491–498.
13. **Guardado-Mendoza, R., Davalli, A.M., Chavez, A.O., Hubbardc, G.B., Dick, E.J., Majluf-Cruz, A., Tene-Perez, C. E., Goldschmidt, L., Hart, J., Perego, C., Comuzzie, A. G., Tejero, M.E., Finzi, G., Placidi, C., La Rosa, S., Capella, C., Halff, G., Gastaldelli, A., DeFronzo, R.A., Folli, F.** Pancreatic islet amyloidosis, beta-cell apoptosis, and beta-cell proliferation are determinants of islet remodeling in type-2 diabetic baboons. PNAS, 2009, v. 106, N33, 13992–13997.
14. **Pearlman, D.A., Case, D.A., Caldwell, J.W., Ross, W.S., Cheatham, T.E. III, DeBolt, S., Ferguson, D., Seibel, G., Kollman, P.** AMBER, a package of computer programs for applying molecular mechanics, normal mode analysis, molecular dynamics and free energy calculations to simulate the structural and energetic properties of molecules. Comp. Phys. Commun., 1995, v. 91, p. 1–41.
15. **Case, D.A., Cheatham, T., Darden, T., Gohlke, H., Luo, R., Merz, K.M. Jr., Onufriev, A., Simmerling, C., Wang, B., Woods, R.** The Amber biomolecular simulation programs. J. Computat. Chem., 2005, v. 26, p. 1668–1688.
16. **Ponder, J.W., Case, D.A.** Force fields for protein simulations. Adv. Prot. Chem., 2003, v. 66, p. 27–85.
17. **Patil, S.M., Xu, S., Sheftic, S. R., Alexandrescu, A.T..** Dynamic α-Helix Structure of Micelle-bound Human Amylin. J Biol Chem., 2009, v. 284, N 18, p 11982–11991.
18. **Maacioni, A., Porcelli, U., Ilangovan, Ramamoorthy, A., Veglia,G.** Conformational prefrrence of amylin nucleation site in SDS micelles: an NMR study. Biopolymers, 2003, v. 69, p 29-41.
19. **Alexandrescu, A. T., Croke, R. L.** (2008) in Protein Misfolding (O'Doherty, C. B., and Byrne, A. C., eds) Nova Science Publishers, Hauppauge, NY.
20. **Apostolidou, M., Jayasinghe, S.A., Langen, R**. Structure of alfa-Helical Membrane-bound Human Islet Amyloid Polypeptide and Its Implications for Membrane-mediated Misfolding. The Journal Of Biological Chemistry, 2008, v. 283, No. 25, p. 17205–17210.
21. **Humphrey, W., Dalke, A. Schulten, K.,** "VMD - Visual Molecular Dynamics" J. Molec. Graphics, 1996, v. 14, p. 33-38.
22. Chemical Computing Group C., Molecular Operative Enviroment (MOE) 2008.
23. Roger Sayle and E. James Milner-White. "RasMol: Biomolecular graphics for all", Trends in Biochemical Sciences (TIBS), September 1995, v. 20, No. 9, p. 374.

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Dmitrijs Lapidus, Salvadors Ventura, Cezars Čaplevskis, Adams Livo, Inta Liepiņa. Amilīna amiloīda atsevišķas beta sloksnes molekulārā dinamika

Amilidozes ir metaboliskas jeb, tā sauktās, konformāciju slimības, ko rada šķīstošu proteīnu atlocīšanās, nepareiza salocīšanās un agregācija nešķīstošās fibrillās, kas nogulsnējas, izspiežot funkcionālās šūnas, vai bloķē starpšūnu sakarus. Amilīns jeb Amiloīdais Polipeptīds (IAPP) ir 37 aminoskābju sekvences hormons, ko izdala aizkuņģa dziedzera β-šūnas kopā ar insulīnu. Amilīna fibrillu nogulsnes aizkuģa dziedzerī izraisa II tipa diabētu. Amilīna rezidiju 10-29 QRLANFLVHSSNNFGAILSS (Amylin 10-29) sešu virkņu beta sloksne tika pētīta ar molekulārās dinamikas (MD) simulāciju periodiskā ūdens kastē ar Amber 9.0 programmu paketi, lietojot f99 spēku lauku un izotermisko-izobārisko ansambli, NTP protokolu (konstanta temperatūra, konstants spiediens un konstants daļiņu skaits). Kopējais Amilīna 10-29 MD simulācijas laiks bija 193 ns.
MD simulācija parādīja, ka a) Amilīna 10-29 ß-sloksne turas kopā galvenokārt ar pamatķēžu ūdeņraža saitēm, b) Amilīna 10-29 ß-sloksni stabilizē sānu ķēžu ūdeņraža saišu mijiedarbība starp rezidijiem Ser^{20} un Asp^{22}, c) Amilīna 10-29 ß-strandi, - izstieptās Amilīna 10-29 virknes tiek salīmētas kopā ar leicīna, izoleicīna un valīna rezidijiem, un ar fenilalanīna rezidijiem, kas, piedaloties asparagīna rezidijiem, veido serdi, ko satur kopā vājas polāras mijiedarbības, d) Amilīna 10-29 ß-sloksnes C-galā ir hidrofobs enkurs no izoleicīna un leicīna rezidijiem Ile^{26}-Leu^{27}, kas varētu saistīt kopā blakus esošās ß-sloksnes ß-slokšņu protofibrillā. Šī mijiedarbība varētu stabilizēt arī atsevišķas ß-sloksnes ß-struktūru, d) Amilīna 10-29 ß-sloksnes rajonā Ser^{19}-Ser^{20}-Asn^{21}-Asn^{22} ß-sloksnei ir W-veida liekums ar dziļāko virsotni uz Ser^{20} rezidiju un seklāko virsotni uz Asn^{22} rezidiju, liekot secināt, ka iespējama arī saliekta ß-sloksne.

Дмитрий Лапидус, Сальвадор Вентура, Цезар Чаплевский, Адам Ливо, Инта Лиепиня. Молекулярная динамика амилоида амилина для одного бета – листа

Амилоидозами являются метаболические болезни или так называемые конформационные болезни, вызванные неправильным фолдингом и агрегацияй растворимых белков в нерастворимыие фибрилы, которые откладываются в тканях, замещая здоровые клетки или блокируя связь между клетками. Амилин или полипептид амилоида (IAPP), состоящий из 37 аминокислот, является гормоном, выделяемым поджелудочной железой вместе с инсулином. Оседание амилина в фибрилы связано с заболеванием диабета второго типа. ß – лист, построенный из шести цепей амилина 10 - 29 QRLANFLVHSSNNFGAILSS (Amylin 10 - 29), был исследован методом молекулярной динамики (МД). ß - лист амилина 10 - 29 был помещён в периодическй ящик воды, состоящий из отдельных молекул воды, и моделирован в течение 193 нс с помощью пакета программ Amber 9.0, в силовом поле F99 с использованием протокола NTP, изотермических-изобарических распределений (постоянная температура, давление и число частиц).
Расчеты МД показывают, что а) ß - структуры амилина 10 - 29 держатся вместе, главным образом, благодаря водородным связям между соседними основными цепями; б) ß - структуру стабилизируют водородные связи между остатками боковых цепей аспарагина и серина (Ser20 и Asp22); в) ß - структуры амилина 10 - 29 склеиваются гидрофобными взаимодействиями остатков лейцина, изолейцина, валина и остатков фенилаланина, которые вместе со остатками аспарагина образовывают кору, связанную слабыми полярными взаимодействиями; г) на С-конце ß - лист амилина 10 - 29 имеет гидрофобный якорь, образованный из остатков лейцина и изолейцина (Ile26 - Leu27), который может быть использован для привязки соседних ß - листов в протофибриле. Это взаимодействие должно стабилизировать ß - структуры отдельных ß - листов; д) на 193 нс в регионе Ser19 - Ser20 - Asn21 - Asn22 ß - лист амилина 10 - 29 имеет форму “W” изгиба с более глубокой вершиной на Ser20 и менее глубокой вершиной на Asn22, указывая на то, что также возможен и изогнутый ß - лист.