Molecular Dynamics Simulation of Interaction of Lysine Dendrigraft of 2nd Generation with Stack of Amyloid Peptides.

I. Neelov, D. Khamidova, V.Bezrodnyi and S.Mikhtaniuk

***Abstract*—In present paper, molecular dynamics simulation is used to study destruction of stack of short amyloid peptide molecules by oppositely charged dendrigraft of 2nd generation. Dendrimers and dendrigraftss are often used in biomedicine for delivery of drugs and other biological molecules. They also could be used as antibacterial, antiviral and antiamyloid agents. Since lysine dendrimers and dendrigrafts are less toxic than many other conventional synthetic dendrimers they were chosen for present study and two systems consisting of 2nd generation dendrigraft and stack of 8 or 16 short amyloid peptide molecules were simulated by the method of molecular dynamics in water. It was demonstrated that lysine dendrigraft destroys both studied amyloid stacks and forms stable complexes with their peptide molecules. The final structures of the complexes in equilibrium state were studied also. It was shown that peptides in complexes stay mainly on the surface of dendrigrafts and do not penetrate into them. The results obtained in present paper could be useful for elaboration in future the anti-amyloid agents for treatment of Alzheimer's disease, since it is believed that one of the sources of this disease is the formation of toxic amyloid oligomers and fibrils.**

***Keywords*—lysine dendrimers and dendrigrafts, amiloid fibrils, computer simulation, molecular dynamics method**

I. Introduction

ALZHeimer's disease is currently one of the most common incurable neurodegenerative diseases. It is characterized by accumulation of amyloid plaques formed by amyloid Aβ peptides in brain tissues [1]. Its primary symptoms begin long before the appearance of serious pathologies and often coincide with symptoms of other nervous system diseases. In treatment of this disease three types of drugs are used: cholinesterase inhibitors (Galantamine, Donepezil and their analogues); drugs that reduce the activity of the glutamate mediator (Memantine); antipsychotic drugs for psychosis and aggression suppressing. This disease in the early stages causes short-term memory disorders, and later leads to long-term memory disorders, speech and cognitive impairment, and ultimately leads to death. Inhibition of beta-amyloid aggregation is one of the promising ways of disease control.

Dendrimers have point-like core and regular star-like branches originated from it. They are widely used in industrial and biomedical applications and in particular as drug and gene delivery systems, as a branched carrier for multiple antigen peptides (MAPs), as antiviral and antibacterial agents. It was experimentally shown that PAMAM and PEI dendrimers can destroy amyloid fibrils [2]. Lysine dendrimers are important class of dendrimers consisting of lysine aminoacid residues as branching repeating units. Recently it was shown that lysine dendrimers also could destroy amyloid fibrils [3].

During last years the similar molecules but with linear core were prepared [4]. They were named dendrigraft because their structure is similar with structure of short dendritic brushes (i.e. short grafted linear polymer with dendritic side chains). Due to their similarity to dendrimers they could be used in the same biomedical application as dendrimer and in particular could be tested as antiamyloid agent.

The goal of present paper is to study the interaction of lysine dendrigraft of 2nd generation and stacks of amyloid peptides in order to understand the mechanism responsible for amyloid fibrils destruction by dendrigraft.

II. Methods and Materials

A. Molecular dynamics method

Molecular dynamics (MD) method is currently one of the best methods for simulation of polymer and biopolymer systems. The method consists in numerical solution of the classical Newton equations of motion for all atoms of the all molecules in the system:

$$F_i = m_i \frac{d^2 r_i(t)}{dt^2} \quad (1)$$

MD is used for detailed study of many different molecules using both detailed full-atomic models as well as more general coarse-grained models. The potential energy of these models usually include valence bonds, valence angles and dihedral angle energy terms as well as van der Waals and electrostatic terms. The definition of parameters set (force-field) for

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adequate description of the molecule properties is challenging and requires the experimental data for these molecules, quantum chemical calculations as well as iterative procedures and a very large amount of computer time. Due to this reason several packages of standard computer programs, in which these parameters are defined for a fairly wide range of molecules become widely used in recent years. Currently the most popular molecular modeling packages for simulation of biopolymer molecular systems consisting of natural monomers (and in particular aminoacid residues) are GROMACS, AMBER, CHARMM, and some others. Our simulation was performed by molecular dynamics method using the GROMACS 4.5.6 software package [5] and one of the most modern AMBER_99SB-ildn force fields [6].

B. Model and Calculation Method

Modeling was performed using the molecular dynamics method for systems consisting of one lysine dendrigraft of 2nd generation with 48 positively charged NH_3^+ groups, and 8 or 16 LVFFAE peptides, water molecules and Cl- and Na+ counterions in a cubic cell with periodic boundary conditions. The initial conformation for peptide with internal rotation angles of φ = –135º, ψ = 135º, θ = 180º was prepared by Avogadro chemical editor. The structures were optimized in vacuum using molecular mechanics with AMBER force field. Further energy minimizations and simulations were performed using the GROMACS 4.5.6 software package and AMBER_99SB-ildn force fields. The potential energy of this force field consists of valence bonds and angles deformation energy, internal rotation angles, van der Waals and electrostatic interactions. The procedure of molecular dynamics simulation used for lysine dendrimers, dendrigrafts and other polyelectolyte molecules has been described earlier in [7-37]. In all calculations the normal conditions (temperature 300 K, pressure 1 ATM) were used. Computing resources on supercomputers "Lomonosov" were provided by supercomputer centre of Moscow State University [38].

The size of dendrigraft and complexes at time *t* was evaluated by the mean square radius of gyration $R_g(t)$ which is defined from:

$$R_g^2(t) = \frac{1}{M} \times \left[\sum_{i=1}^{N} m_i \times \left| r_i(t) - R \right|^2 \right] \qquad (2)$$

where R – is the center of mass of subsystem, r_i и m_i – coordinates and masses of i-atom correspondingly, N – is the total number of atoms in subsystem, M is the total mass of dendrigraft. This function was calculated using *g_gyrate* function of GROMACS software.

Radial distribution of density p(r) of atoms in dendrigraft and complexes as well as distribution of ion pairs were calculated using g_rdf function of the GROMACS package.

To calculate the coefficient of translational mobility of dendrigraft and complexes, the time dependence of the mean square displacements of the centers of inertia (MSD) of corresponding sub-system, were calculated. MSD was calculated using g_msd function of GROMACS.

III. Results and Discussion

Snapshots of systems consisting of dendrigraft, peptides, ions and water during simulation are shown on Fig. 1 (water molecules are not shown for clarity). It is clearly seen that at the beginning of process (Fig. 1, a, d) stack of peptide molecules is rather far from dendrigraft. After 30ns (Fig. 1, b, e) only part of peptide molecules was adsorbed by dendrigraft. And at 100 ns (Fig. 1, c, f) all peptide molecules are adsorbed on the surface of dendrigraft. Atoms of dendrigraft molecule is shown as beads with diameter equal to their van der Waals radii. Valence bonds of various peptides are shown with lines and backbone of each peptide is shown by thick line.

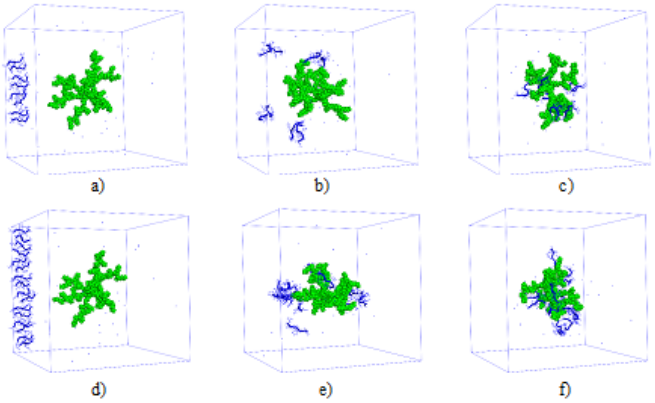


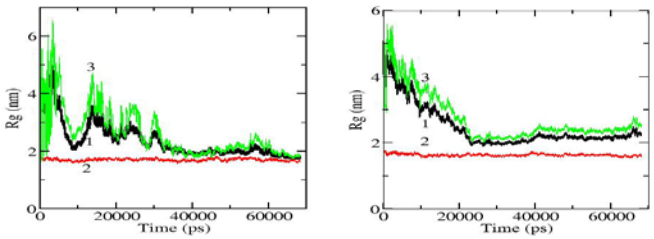
Fig. 1.Stages of the destruction of amyloid stack by DG2 dendrigraft and dendrigraft-peptide complex formation (initial, intermediate and final): system of DG2 dendrigraft and 16 peptides at t = 0 (a), t = 30 ns (b), t = 100 ns (c); system of DG2 dendrigraft and 16 peptides at t = 0 (d), t = 30 ns (e), t = 100 ns (f)

$$\left\langle \sum_t \Delta r^2(t + k\Delta t) \right\rangle = \left\langle \sum_t (r(t + k\Delta t) - r(t))^2 \right\rangle = 6Dt \qquad (3)$$

A. Destruction of stack of amyloid peptides by dendrigraft and dendrigraft-peptide complex formation

Radius of gyration of subsystem consisting of dendrigraft and peptide molecules should decrease during stack destruction and complex formation. In the beginning of time all peptide molecules are far from dendrigraft (see Fig.1) and after that peptide become closer and closer to dendrigraft surface and first part (t < 30-40 ns) of time dependence of gyration radius R_g really demonstrate such behavior (Fig. 2). From Fig. 2a it can be seen that dendrigraft forms complex

with 8 molecules of peptide within 30-40 ns. From Fig. 2b it can be seen that dendrigraft forms complex with 16 peptides also within 30-40 ns (but fluctuation of Rg during equilibration process in this case are smaller). After that the complex size R_g only slightly fluctuate but its average value practically does not change with time. It means that after this time all peptide molecules already seat on dendrgigraft surface. Therefore, we can assume that after 40 ns the system is practically in equilibrium state.

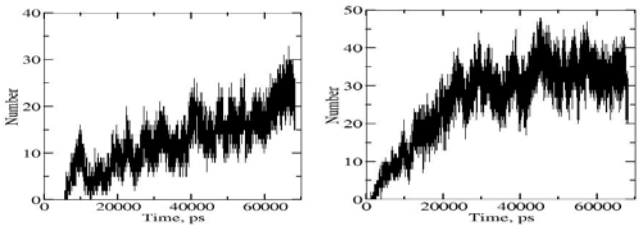


a) b)

Fig. 2. Time dependence of gyration radius of dendrigraft-peptides subsystem during destruction of amyloid stack and dendrigraft-peptides complex formation: a) DG2 and 8LVFFAE; b) DG2 and 16 LVFFAE where 1-size of complex, 2- size of dendrigraft and 3-size of peptide relatively center of mass of dendrigraft.

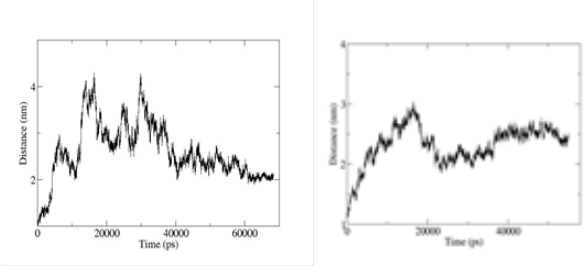
Another quantity that can characterize the process of amyloid stack destruction by dendrigraft and complex formation is the total number of hydrogen bonds (N) between dendrigraft and peptide molecules. The dependence of this value on time is shows on Fig. 3 and demonstrates how the number of hydrogen bond contacts between dendrigraft and peptides increases during stack destruction and comlex formation. This value was calculated using g_hbonds function from GROMACS package.

From Fig. 3 it can be concluded that first system reaches equilibrium (plateau) after 40 ns and second system reaches equilibrium also after practically the same time. It correlates with the results of the inertia radii balance presented in Fig. 2. The number of hydrogen bonds between peptides and dendrigrafts in equilibrium state shows how tightly peptides associate with dendrigraft. The average hydrogen bonds number in equilibrium state (t > 40 ns) for the first complex is close to about 15 and for the second complex is close to 30.



a) b)

Fig. 3. Time dependence of dendrigraft-peptides hydrogen bond number (N) during destruction of amyloid stack and dendrigraft-peptides complex formation: a) DG2 and 8LVFFAE; B) DG2 and 16LVFFAE.

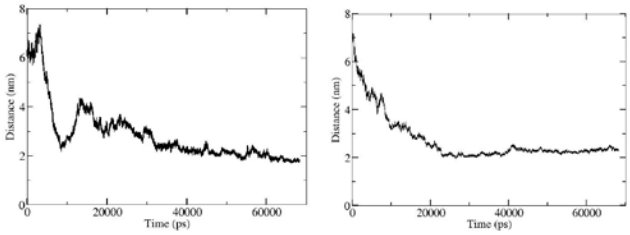


a) b)

Fig. 4. Changes in distances between neighbouring amyloid peptides during destruction of amyloid stack and dendrigraft-peptides complex formation: a) DG2 and 8 LVFFAE; b) DG2 and 16 LVFFAE.

The distance between peptide molecules in amyloid stack (Fig.4) is important characteristic of its stability. In particular for the first system (DG2 and 8 peptide molecules) the distance between peptides for the first 30-40 ns (during the peptide stack destruction) increases. After 30-40 ns it decrease and after that the function only fluctuates slightly. It means that interaction with complex is not tight enough and peptides can leave and return to the stack. In second case (DG2 and 16 peptide molecules), at the beginning, there is also a large increase in distances between the neighboring peptides of the stack. It means that in both systems at small times (0< t <30-40ns) the destruction of amyloid stack occurs and peptides became separated from each other. After 30-40ns this separated peptides become attracted by dendrigraft and distance between them start to decrease and after that go to plateau.

Similar information could be obtained from time dependence of distance between dendrigraft and peptides (Fig.5). This value characterize mainly not peptide stack but dendrigraft-peptide complex. In the beginning of time all peptides are far from dendrigraft (see Fig.1). After that peptide become closer and closer to dendrigraft surface. In case of G2 and 16 LVFFAE the peptides are attracted by dendrigraft in 30-40 ns.



a) b)

Fig. 5. Changes in distances between dendrigraft and peptides during destruction of amyloid stack and dendrigraft-peptides complex formation: 1 – DG2 and 8 LVFFAE; 2 – DG2 and 16 LVFFAE.

In the second case the behavior is similar: decrease at time less than 30-40 ns and tthe distance does not change further with time at t>40ns It means that we obtained almost equilibrium dendrigraft-peptide complex at time *t*>40 ns.

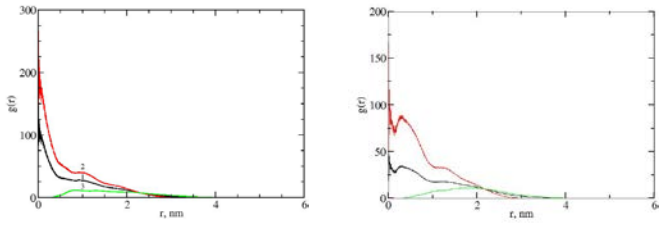
B. Modelling of equillibrium state of dendrigraft-peptide complex

In equilibrium state the mean squared radius of gyration *Rg* (averaged through equilibrium part of trajectory t>40ns) of the first complex (D*G2* and 8 LVFFAE) is 1.14 times larger, than the size of the dendrigraft in first complex. The mean squared radius of gyration *Rg* of the second complex (D*G2* and 16 LVFFAE) is 1.32 times larger, than the size of the dendrigraft DG2 in second complex (Tab. 1). It is quite natural, since size of complex correlates with its larger molecular weight (and volume) of the complexes in comparison with individual dendrigraft. But the size dendrigraft itself in second complex is smaller than if first complex. It means that adsorption of greater number of oppositely charged peptides compress the dendrigraft core of complex. The shape of both complexes can be characterized by their tensor of inertia main component ratio (R_g^{11}, R_g^{22}, R_g^{33}), that are in Tab. 1. For example, in the simplest case, anisotropy can be characterized by ratio R_g^{33} / R_g^{11}. This ratio for DG2 itself in first complex (DG2 dendrigraft with 8 peptides) is 1.23 in second complex (DG2 dendrigraft with 16 peptides) is 1.20 and for all atoms of first complex is 1.27 and for all atoms of 2nd complex of is 1.40. Thus, the anisotropy of our complexes is rather small and only slightly greater in comparison with the anisotropy of the dendrigrafts in them.

Table 1. Eigenvalues R_g^{11}, R_g^{22}, R_g^{33} of tensor of inertia in dendrigraft and dendrigraft - peptide complex

System	R_g^{11}, nm	R_g^{22},nm	R_g^{33}, nm	R_g, nm
Dendrigraft in DG2+8LVFFAE	1,23	1,41	1,51	1,70
Dendrigraft in DG2+16LVFFAE	1,21	1,31	1,45	1,63
DG2 +8LVFFAE	1,38	1,60	1,76	1,94
DG2+16LVFFAE	1,44	1,80	2,01	2,16

Information about the internal structure of the equilibrium complex could be obtained using radial density distribution of different groups of atoms relatively center of inertia both for the complexes themselves and for their individual components (Fig. 6).



a) b)

Fig. 6. Radial distribution p(r) density (not normalized) of complexes DG2 and 8 peptides (a); DG2 and 16 peptides (b). Distribution curves: all atoms of complex (1); dendrigraft atoms (2); peptide atoms (3).

The data demonstrates that in both subsystems dendrigraft (curve 2) is located in the center of the complex and peptides (curve 3) are mainly on the surface of complex. At the same time, some fraction of peptides could slightly penetrate into outer part of dendrigraft.

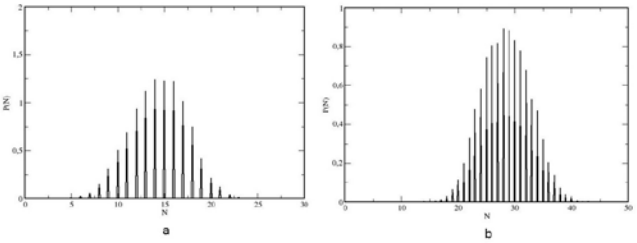
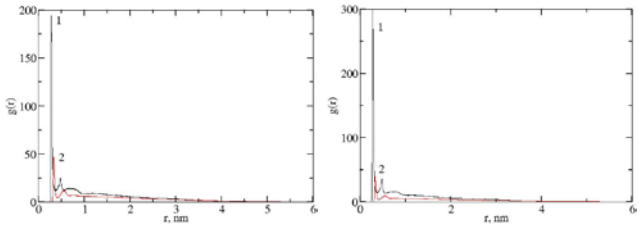


Fig. 7. The distribution function P(N) of hydrogen bonds number N of complex: a – DG2 and 8LVFFAE, b – DG2 and 16 LVFFAE

The distribution function P(N) of number N of hydrogen bonds between dendrigraft and peptides (Fig. 7) has a peaks of numbers of bonds at 14 (Fig. 7a) and 28 (Fig. 7b) that is close to the average value equal to 15 and to 30 from Fig.3 and is quite symmetrical (fluctuations in hydrogen bonds number are for the first system in the range of 6-22 and for the second system in the range of 16-40).

The other characteristic of interaction between dendrigraft and peptides (1) in equilibrium dendrigraft-peptide complex is the distribution of ion-pairs number between their oppositely charged groups. Fig. 8 shows the dependence of ion-pairs number on the corresponding distance between pairs of charges of dendrigraft and peptides in our complex.

It is seen that there is very sharp peak of ion pairs between dendrigraft and peptide oppositely charged groups in both cases, at the distance corresponding to the direct contact between (NH_3^+) groups of dendrigraft and (COO^-) groups of the glutamic acid in peptide molecules (Fig 8, curves 1). At the same time, NH_3^+ groups of dendrigraft form much fewer ion pairs with chlorine ions Cl^- (Fig 8, curves 2).

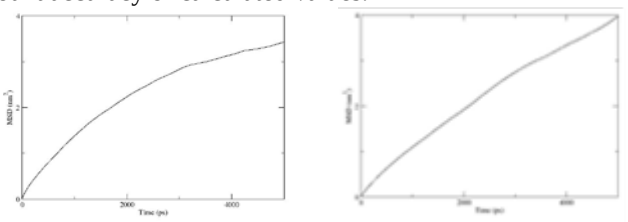


a) b)

Fig. 8. Radial distribution function of ion pairs: a) complex of DG2+8LVFFAE and b) complex of DG2+16 LVFFAE, 1- NH_3^+ groups of dendrigraft and COO^- groups of peptide molecules; 2 - NH_3^+ groups of dendrigraft and Cl^- ions;

To evaluate the translational mobility of our complex, the time dependence of the mean square displacement of the

center of inertia (MSD), was calculated (Fig. 9). MSD was calculated using g_msd function of GROMACS. Coefficients of translational diffusion of the complexes were obtained from the slope of this time dependence and were equal to (0,13 ± 0,04) $\times 10^5$ sm^2/s and (0,14 ± 0,02) $\times 10^5$ sm^2/s, correspondingly., i.e. were practically the same taking into account accuracy of calculated values.



a) b)

Fig. 9. Mean square displacement of the center of inertia: 1 - complex of G2 and 16 LVFFAE; 2 - G3 and 16 LVFFAE

IV. Conclusion

The process of destruction of the stacks consisting of 8 or 16 amyloid peptides LVFFAE (with charge of each peptide equal -1) by an oppositely charged lysine dendrigraft of 2nd generation (having charge equal to 48), the complex formation and the structure of final equilibrium complex were studied. It was shown that the amyloid fibrils can be destroyed in 20-30 ns, and stable dendrigraft-peptide complexes can be formed after 30-40ns in both cases.

The radial distribution function of atoms numbers in complexes shows that dendrigraft is located in the center of the complexes and peptides are mainly on their surfaces. The strong electrostatic interactions between dendrigrafts and peptides in our complexes (contact of positively charged NH_3^+ groups of dendrigraft and carboxyl groups of glutamic acid in peptides) were demonstrated. At the same time, we found that NH_3^+ groups of dendrigraftes form much fewer ion pairs with chlorine counterions.

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