Complexes of Lysine Dendrimer of 2nd/3rd Generations and Semax Peptides. Molecular Dynamics Simulation

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Abstract: - Complexes of lysine dendrimer and nootropic Semax peptides were studied using molecular dynamics simulation. These dendrimers were used for drug and other molecules delivery to different cells. It was shown earlier that dendrimers and in particular lysine dendrimers could penetrate blood brain barrier. In present paper three systems containing lysine dendrimers of 2nd and 3rd generations and 8, 16 or 24 oppositely charged Semax peptides were studied. It was obtained that lysine dendrimers of both generations attracts Semax peptides and forms stable nanocomplexes with peptides. The sizes and structures of these nanocomplexes were investigated. These complexes can be used in future for delivery of Semax peptides to brain since these peptides have significant neuroprotective effects.

Key-Words: - lysine dendrimer, Semax peptides, computer simulation, molecular dynamics

1 Introduction

Dendrimers are highly-branched macromolecule with a “tree-like” structure. They usually consist of three main type of units: a core, branches and terminal groups

Dendrimers are widely used in many medical applications as drug and gene delivery systems, as a branched carrier for multiple antigen peptides (MAPs), as antiviral and antibacterial agents. They are also promising anti-amyloid agents for treatment of neurodegenerative diseases (Alzheimer's, Parkinson's and etc.).

Dendrimer could be synthesized by divergent and convergent methods. In both cases the dendrimer size, its molecular weight and number of its terminal groups can be controlled.

Dendrimers monodispersity, nanoscale size and polyvalency make them effective instrument for drug encapsulation. They have unique properties because of their spherical shape and presence of internal cavities. In order to use dendrimers as biological agents, they also should be non-toxic, non-immunogenic, able to cross cell membranes and other bio-barriers, as well as stay in blood circulation for the time required to get a clinical effect on patients.

In present simulation we used dendrimers of 2nd and 3rd generations (see Fig.1). Therapeutic Semax peptide was selected in our study as a model peptide because it belongs to a class of regulatory peptides and has an antioxidant, antihypoxic and neuroprotective properrties. Semax peptide is used for acute ischemic stroke prevention, during traumatic brain injury treatment, recovery of a patients after a stroke, in the case of optic nerve disease and glaucoma optic neuropathy. Peptide and its amino acid sequence are shown on Fig. 1.

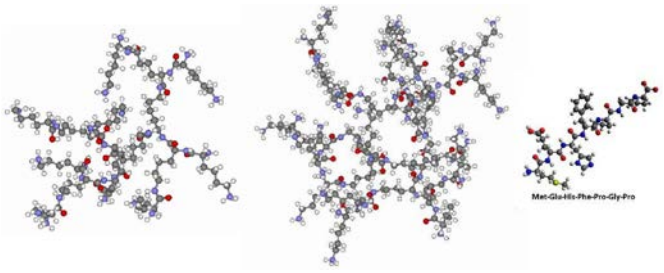

Fig. 1. Lysine dendrimer of 2nd, 3rd generation and one Semax peptide

The use of dendrimers as potential drug carriers has many advantages (see for example, [2]). In particular dendrimers improve the solubility of drugs in water, increase the time of drug circulation in blood, and could be used for targeted delivery of drugs to specific tissues. They also could improve the transfection and crossing different biological barriers.

It is known that electrostatic interaction are very important for the complex formation. In the case of lysine dendrimers and Semax peptides there are electrostatic interaction between multiple positively

charged end groups of dendrimer (NH_3^+) and small negative charge of each peptide. Hydrogen bonds between dendrimer and peptide and hydrophobic interactions between their nonpolar groups are also important.

The goal of this paper is to study and compare the interaction between lysine dendrimers of second and third generations with different number of therapeutic Semax peptides using molecular dynamics method to check whether a dendrimer can form a complex with Semax peptides and thus could be used for delivery of these peptides into cells.

2 Methods and Materials

2.1 Molecular dynamics method

Molecular dynamics (MD) method is currently the main method for computer 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. It was used first in the mid-fifties of the last century [3] for two-dimensional modeling of hard disks system (2D-model of a monoatomic gas), and then was used to simulate a variety of liquids, including water [4, 5]. In 1972 this method was first applied to the simulation of a simple model of a linear polymer chain consisting of atoms connected by rigid bonds [6]. In 1975 the dynamics of short n-alkanes was studied [7]. In subsequent years MD was used for detailed study of many specific molecules using both detailed full-atomic models as well as more general coarse-grained models (see for example, [8]). The potential energy of these models usually include valence bonds, valence angles and dihedral angle energies as well as van der Waals and electrostatic energies. The definition of parameters set adequately describing the test molecule properties (force-field) is challenging and requires the experimental data for these molecules, quantum chemical calculations as well as iterative procedures and a very large amount of machine time. These calculations can be made only by large groups of specialists. 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 are GROMACS, AMBER, CHARMM, and some others. Our simulation was performed by molecular dynamics method using the GROMACS 4.5.6 software package [9] and one of the most moderrn AMBER_99SB-ildn force fields [10].

2.2 Model and Calculation Method

Computer simulation was performed using the molecular dynamics method for systems consisting of one lysine dendrimer of second or third generation with positively charged NH3+ end groups and 8, 16 or 24 Semax peptides (with charge -1 each). These molecules were placed in water box (cubic cell with periodic boundary conditions) with chlorine counterions. The initial conformation of dendrimer was taken from the end of long simulation run of dendrimer in water without peptides. For peptides the initial conformation with internal rotation angles of $\varphi = -135^o$, $\psi = 135^o$, $\theta = 180^o$ was prepared using Avogadro chemical editor. The structures of peptides were first optimized in vacuum using molecular mechanics and AMBER force field. Further energy minimization and simulations of whole system was 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 both for lysine dendrimers and for polyelectolytes has been described earlier in [11-23]. In all calculations the normal conditions (temperature 300 K, pressure 1 ATM) were used. Computational resources on supercomputers “Lomonosov” were provided by supercomputer centre of Moscow State University [24]

3 Results and Discussion

Snapshots of Semax peptides and dendrimers of 2nd and 3rd generation with peptides, ions and water during simulation with equal time intervals were prepared using MD trajectory obtained in simulation. Some of them are shown on Fig. 2

(water molecules are not shown for clarity). It is clear seen that at the beginning of the process (Fig. 2) all peptide molecules are far from each other (a) and dendrimers (b, c). After 100 ns some part of peptide molecules are connected to each other by electrostatic bonds (Fig. 2, a). In case of systems with dendrimers (Fig. 2, b, c) all peptide molecules in all systems are on their surface.

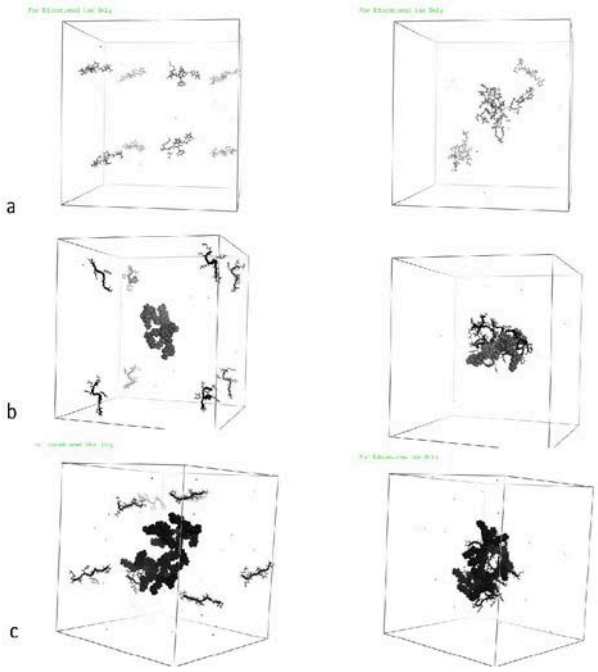

Fig. 2. Stages of Semax and dendrimer-peptide complex formation (initial and final): 8 peptides (a); system of dendrimer G2 and 8 peptides (b); system of dendrimer G3 and 8 peptides (c). Atoms of dendrimer molecule are shown as beads with diameter equal to their van der Waals radii. Valence bonds inside peptides are shown with thin lines. Backbones of different peptides are shown by thick lines of different colours.

To characterize the size of the systems the gyration radius $Rg^2(t)$ was used. It was calculated using:

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

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

2.1 Modeling of Equilibrium Process Establishment

The decrease of gyration radius R_g(t) at the beginning of calculation describes the process of transition from system consisting of separate molecules to complex (Fig. 3). It can be seen that G2 dendrimer and 8, 16, 24 peptides form complexes in all cases within 20-40 ns. At times greater than 20-40 ns the size of complexes R_g(t) practically do not change with time. Complexes of G3 dendrimer with 8, 16, 24 molecules of Semax form for the similar time (i.e. within 20-40 ns). After this the sizes of the complexes slightly fluctuate but do not change with time . Therefore, we can assume that after this time the systems are in equilibrium state. Fluctuation of complexes are usually smaller for complex with G3 dendrimer in comparison with complexes with G2 dendrimers.

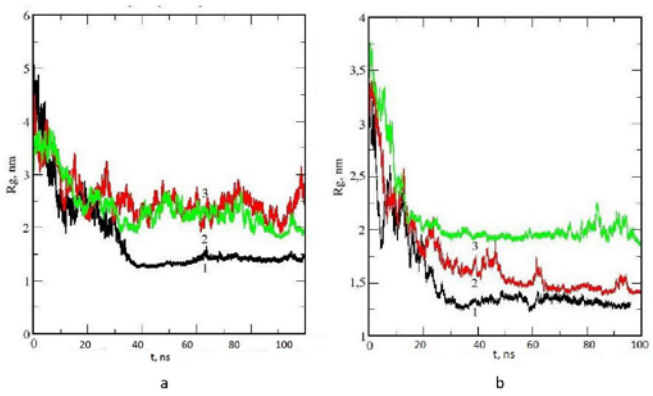

Fig. 3. Time dependence of gyration radius. System of dendrimer G2 (a) and G3 (b) with 8 Semax peptides (1); 16 Semax peptides (2); 24 Semax peptides (3)

Another quantity that can characterize the rate of complex formation is the total number of hydrogen bonds (N) between dendrimers and peptides. The dependence of this value on time is shows on Fig.4 and it demonstrates how the number of specific contacts between them increases during complex formation (times smaller than 20-40 ns). This function was calculated using g_hbonds function of GROMACS.From Fig. 4 it can be concluded that G2+8Semax system (Fig. 4, a, graph 1) reaches equilibrium (plateau) after 40 ns. In

case of G2 with 16 and 24 Semax, systems (Fig. 4, a, graphs 2 and 3) reach equilibrium at 20 ns.

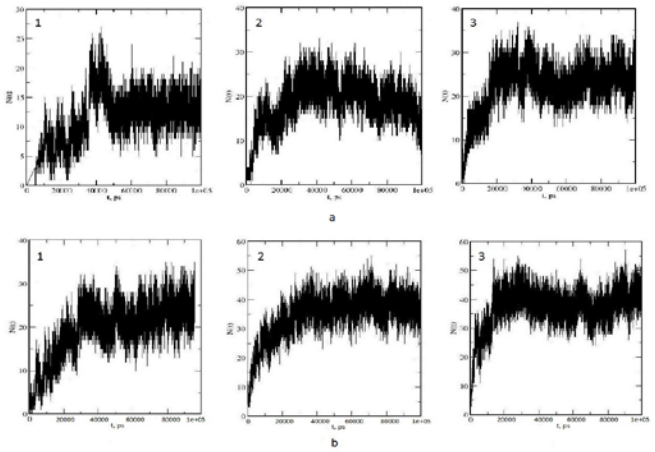

Fig. 4. Time dependence of hydrogen bonds number (N) during the complex formation: G2 (a) and G3 (b) with 8 Semax (1), 16 Semax (2) and 24 Semax (3)

System of G3 with 8 Semax reaches equilibrium after 30 NS. Thus, dependences of number of hydrogen bonds on times demonstrate that complexes between dendrimer and Semax peptides forms in all systems in 20-40 ns. This result correlates well with the results for the gyration radius (see Fig. 3).

3.2 Modeling of the equilibrium state

In equilibrium state the size of the complex with G2 and 8 Semax peptides is larger than the size of dendrimer, and the size of the complex G2 and 16 Semax is slightly larger than the size of the first one (see Tab. 1). The size of the complex G2 and 24 Semax is also larger than the size of the previous ones. In equilibrium state the size of the complex consisted of G3 and 8 Semax peptides is also larger than the size of dendrimer, and smaller than the size of the complex with G3 and 16 Semax. The size of the complex G3 and 24 Semax is also larger than the size of the previous ones. It is quite natural, since it correlates with the molecular weight of the complexes which increases increase proportional to number of peptides in 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.

The values of anisotropy obtained by this method are presented in Tab. 2. It could be seen that the molecular weight dependences of the anisotropy for our systems are not monotonous. In case of G2 dendrimer with 16 Semax, the largest component of inertia tensor Rg33 is 1.5 times larger than this component in complex with 8 peptides and is 1.13 times smaller than in complex with 24 peptides.

Table 1. R_g^{11}, R_g^{22}, R_g^{33}, R_g Means square values of components of tensor of inertia and gyration radius OF dendrimer and complexes

System	R_g^{11} (nm)	R_g^{22} (nm)	R_g^{33} (nm)	R_g (nm)
Dendrimer (*G2*)	0.64	0.972	1.084	1.124
G2 & 8 Semax	0.964	1.128	1.308	1.424
G2 & 16 Semax	1.374	1.578	1.958	2.298
G2 & 24 Semax	1.512	2.058	2.214	2.354
Dendrimer (*G3*)	0.98	1.224	1.316	1.444
G3 & 8 Semax	1.044	1.308	1.452	1.581
G3 & 16 Semax	1.236	1.340	1.512	1.663
G3 & 24 Semax	1.304	1.656	1.780	1.944

At the same time, the smallest component Rg^{11} of the complex with 16 peptides is just in 1.05 times larger than that component in complexes with G2 and 8 peptides and in 1.21 times smaller than in complex consisted of G2 and 24 peptides. In case of G3 dendrimer with 16 Semax molecules, the largest component of inertia tensor Rg^{33} is 1.16 times smaller than this component in complex with 8 peptides and is 1.13 times smaller than in complex with 24 peptides. At the same time, the smallest component Rg^{11} of the complex with 16 peptides is just in 1.05 times larger than that component in complexes with G3 and 8 peptides and in 1.11 times smaller than in complex consisted of G3 and 24 peptides. The results obtained mean that there is no systematic dependence of anisotropy on size of complex but the anisotropies for all complexes fluctuate between the values 1.2 and 1.5.

Table 2. The values of anisotropy of shape R_g^{33}/R_g^{11} for dendrimer and for its two complexes with peptides

System	G2	G3
Dendrimer	1.69	1.34
Dendrimer +8 Semax	1.35	1.39

Dendrimer +16 Semax	1.42	1.22
Dendrimer +24 Semax	1.46	1.36

Information about the internal structure of the equilibrium complex could be obtained using radial density distribution of different groups of atoms relatively centre of inertia of system.

This radial distribution function (calculated using *g_rdf* function of GROMACS without normalisation) are shown on Fig. 5-6. Fig 5 demonstrates that dendrimer G2 (curve 2, Fig.5) is located in the center of the complexes (at small values of r) and 8 peptides in first system (curve 1, Fig. 5a) could penetrate to its center. But peptides in second and third systems (curve 1, Fig. 5b, 5c) are mainly on the surface of complex in all systems. It is better seen for system with 16 and even more clear for system with 24 peptides. Curve 3 (for whole system) demonstrates behaviour average between curve 1 and curve 2.

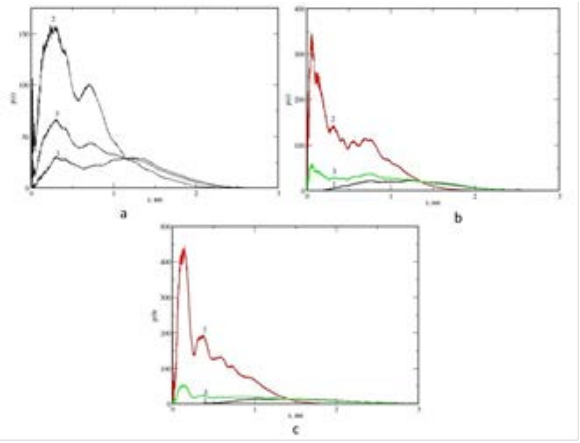

Fig. 5. Radial distribution p(r) curves: dendrimer G2 and 8 Semax (a), dendrimer G2 and 16 Semax (b), dendrimer G2 and 24 Semax (c). Distribution curves: peptide atoms (1); dendrimer atoms (2); all atoms of complex (3)

Fig. 6 demonstrates that dendrimer G3 (curve 2, Fig. 6) in all systems is mainly at the centre of complex. Peptides (curve 1, Fig. 6a) in first complex could penetrate to centre of complex while in second and third complexes (Fig.6a, 6b) with 16 and 24 peptides they are mainly on the surface of dendrimer (see curve 1, Fig.6b,c) as it is in complex with G2 dendrimers (Fig.5b,c).

The number of hydrogen bonds between peptides and dendrimers shows how tightly

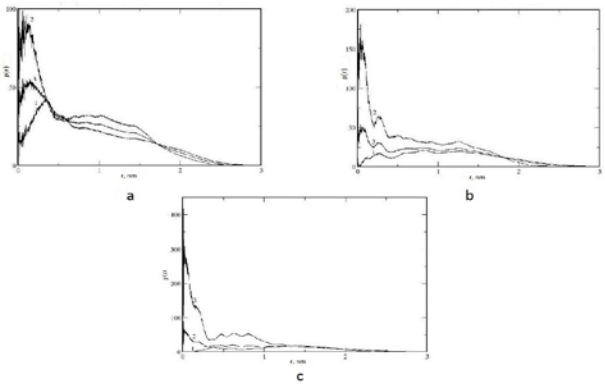

Fig. 6. Radial distribution p(r) curves: dendrimer G3 and 8 Semax (a), dendrimer G3 and 16 Semax (b), dendrimer G3 and 24 Semax (c). Distribution curves: peptide atoms (1); dendrimer atoms (2); all atoms of complex (3)

Table 3. The number of hydrogen bonds (Hb) between dendrimers and peptides

System	Number of Hb
G2 +8 Semax	15
G2 +16 Semax	20
G2 +24 Semax	25
G3 +8 Semax	23
G3 +16 Semax	39
G3 +24 Semax	60

peptides are associated with dendrimer. From Fig. 4 it follows that average hydrogen bonds number in equilibrium state (t > 30 ns) for G2 + 8 and G3 + 8 Semax complexes is close to 15 and 23 respectively. The values for other systems are represented in Tab. 3. The ratio of average number N of H-bonds in complex of G2 with 8 Semax and G2 with 16 Semax is 1.33 and in G2 with 16 Semax and G2 with 24 Semax is 1.25. The same ratio in complex G3 with 8 Semax and G3 with 16 Semax is 1.7 and for G3 with 16 Semax and G3 with 24 Semax is 1.5.smaller than 1.5, it can be concluded, that peptides in systems with 16 peptides are associated with dendrimer by H-bonds not so strong as in systems with 8 peptides. Also, peptides in systems with 24 peptides are associated with dendrimer by H-bonds not so strong as in systems with 16 peptides.

The distribution function of hydrogen bonds number (Fig. 7) shows how the number of hydrogen bonds in the equilibrium state can fluctuate relative to the average value. We obtained that the resulting function in all complexes has a peak at numbers of bonds that are close to the average (13, 20 and 23 in case of G2 dendrimer with Semax; and 23, 39 and 60 in case of G3 dendrimer with Semax) and thus are quite symmetrical. Fluctuations in hydrogen bonds number for the system with G2 and 8 peptides are in the range of 5-20, for the system with G2 and 16 peptides are in the range of 10-30, for the system with G2 and 24 peptides are in the range of 15-35. Fluctuations in hydrogen bonds number for the system with G3 and 8 peptides are in the range of 15-33, for the system with G3 and 16 peptides are in the range of 27-49 and for the system with G3 and 24 peptides are in the range of 27-53. The increase of fluctuations of number of H-bonds between dendrimer and peptides with number of peptides in the complex is also support the conclusion that the association of peptide with dendrimer due to H-bonds is the stronger in the systems with 8 peptides and the weaker in the systems with 16 and 24 peptides.

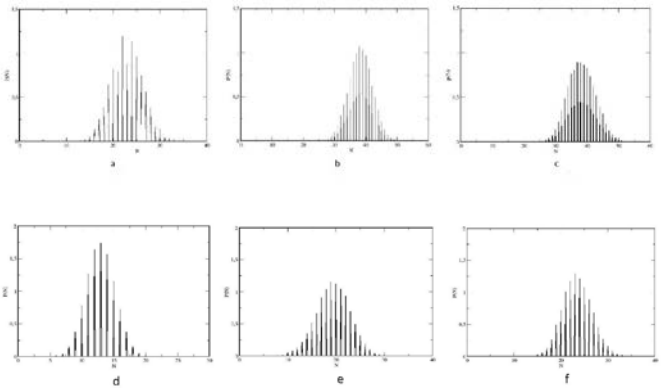

Fig. 7. The distribution function P(N) of hydrogen bonds number N of complexes: complex G3 and 8 Semax (a); complex G3 and 16 Semax (b); complex G3 and 24 Semax (c); complex G2 and 8 Semax (d); complex G2 and 16 Semax (e); complex G2 and 24 Semax (f)

The other characteristic of interaction between dendrimer and peptides in complex is the distribution of ion pairs number between the positively charged groups of dendrimer and negatively charged groups of peptides. Fig. 8 shows the dependence of ion pairs number on the distance between dendrimer and peptides in all complexes. It is seen that in the complexes there is a sharp peak, corresponding to the direct contact between positively charged groups (NH_3^+) of dendrimer and negatively charged groups (COO^-) of the glutamic acid in peptides. In case of complex of G2 with 8 peptides (curve 1) the peak was approximately 2.34 times larger than the peak of G2 with 16 peptides (curve 2) and 2.3 times larger than the peak of G2 with 24 peptides (curve 3) . It confirms our earlier results about more close contact of peptides and dendrimer in first system with 8 peptides.

In case of complex of G3 with 8 peptides (Fig. 8, curve 1) the peak was approximately 1.8 times larger than the peak of G3 with 16 peptides (Fig. 8, curve 2) and 1.3 times larger than the peak of G3 with 24 peptides (Fig. 8, curve 3) . It confirms again our earlier results about more close contact of peptides and dendrimer in system with 8 peptides.

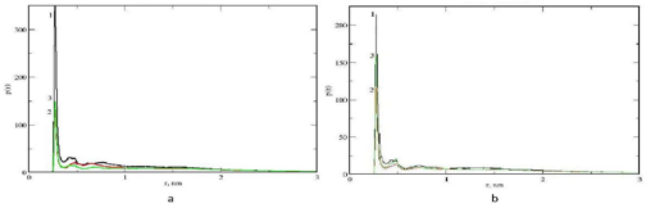

Fig. 8. Function of ion pairs radial distribution: a – NH_3^+ groups of dendrimer G2 and COO^- groups of peptides, b - NH_3^+ groups of dendrimer G3 and COO^- groups of peptides. 1 – dendrimer + 8Semax, 2 – dendrimer + 16Semax, 3 – dendrimer + 24Semax.

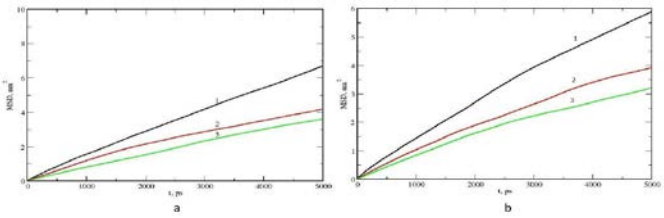

Fig. 9. Mean square displacements of the centres of inertia complex of G2 (a) and G3 (b) with 8 Semax (1); 16 Semax (2); 24 Semax (3)

To evaluate the translational mobility of our systems, the time dependences of the mean square displacement (MSD) of the center of inertia of the systems were calculated (Fig. 9). MSD and corresponding diffusion coefficients were calculated using g_msd function of GROMACS.We have found that the dependence of MSD function on time is almost linear in some interval of time t in double logarithm coordinates (not shown). It means that in this interval the motion of complex is the diffusion-like motion (see Fig.9). Coefficients of translational diffusion of the complexes were determined from

the slope of the time dependences of MSD for all three systems (Tab. 4).

Table 4. Diffusion coefficients for dendrimer-peptide complexes

System	$D \times 10^5$ (sm^2/s)
G2 and 8 Semax	0.35 ± 0.13
G2 and 16 Semax	0.12 ± 0.03
G2 and 24 Semax	0.11 ± 0.02
G3 and 8 Semax	0.17 ± 0.02
G3 and 16 Semax	0.11 ± 0.05
G3 and 24 Semax	0.10 ± 0.03

It was shown that translational diffusion coefficient of the complex with a G3 dendrimer and 8 peptides is approximately 1.54 times larger than that of the complex with 16 peptides. Since the ratio of inertia radii R_g of the second complex (1.66 nm^2) and first complex (1.58 nm^2) is close to 1.05, the additional differences can be explained by the fact that the anisotropy of shape of complex with G3 and 16 Semax is larger, or that a larger number of water molecules are attached to the surface of second complex. As the anisotropy of shape of two complexes differ only slightly (1.05 times), we can chose only our second guess. To check it, we calculated number of hydrogen bonds between molecules, that form our complexes, and water. For G3 and 8 Semax complex the number of such hydrogen bonds was equal to 275, for G3 and 16 Semax it is equal 415 and for G3 and 24 Semax it is equal 561. The ratio of these values for G3 and 16 Semax and G3 and 24 Semax near 1.5. So the greater difference in hydrodynamic radii than for inertia radii for smaller complexes can be explained at least partly by greater number of water molecules associated with larger complex. The ratio of hydrodynamic radii for G3 with 16 Semax and G3 with 24 Semax complexes is close to ratio of their inertia radii which is in agreement with smaller ratio of hydrogen bond numbers for second and third complexes.

Translational diffusion coefficient of the complex with a G2 dendrimer and 8 peptides is approximately 2.9 times larger than that of the complex G2 with 16 peptides. Since the ratio of inertia radii R_g of the complex consisted of G2 and 16 Semax (2.29 nm^2) and complex consisted of G2 and 8 Semax (1.42 nm^2) is close to 1.6, the additional differences can be explained by the fact that the anisotropy of shape of complex with G2 and 16 Semax is larger, or that a larger number of water molecules are attached to the surface of second complex. Our calculations shows that the second factor take palce as it was in case of G3 complexes.

4 Conclusion

The process of complexes formation by lysine dendrimers of 2nd and 3rd generation and therapeutic Semax peptides and the equilibrium structure of complex were investigated by the method of molecular dynamics simulation. It was shown that dendrimer-peptide complexes formation occurs rather quickly (in 20-40 ns). The equilibrium size (radius of gyration) and the anisotropy of all complexes were rather close to each other. The radial distribution function of atoms in all complexes shows that in all cases dendrimer is mainly inside the complex, while the peptides are mainly on its surface. The number of hydrogen bonds and ion pairs per peptide molecule in complexes with 16 and 24 peptides was smaller than in complex with 8 peptides for complexes with both dendrimers. It means that dendrimer and peptides contacts are less strong in the second and third complexes with higher amount of peptides.

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