Interaction of Lysine Dendrimers with Therapeutic Peptides. Molecular Dynamics Simulation.

I. Neelov, E. Popova, D. Khamidova, I. Tarasenko

Abstract—Lysine dendrimers are highly branched molecules. They are often used for drug and other molecules delivery to different target cells. In present study the properties of complexes of lysine dendrimers with two types of therapeutic peptides (Semax and Epithalon) were compared using molecular dynamics. Our simulation demonstrates that the lysine dendrimer form complexes with both types of therapeutics peptides. It was shown that combination of two types of interactions (electrostatic and hydrophobic) result in complex formation in all cases – electrostatic and hydrophobic. It was also demonstrated, that electrostatic interactions between dendrimer and peptides in all complexes are stronger than hydrophobic. Structures of the complexes were investigated and it wa shown that decrease of electrostatic interactions leads to the destruction of the complex and the release of peptides from it.

Keywords—lysine dendrimers, Semax, Epithalon, computer simulation, molecular dynamics method.

I. Introduction

DENDRimers are regularly branched molecules which have a spherical shape and many terminal groups available for modification. Since the early 80s of the last century, when the first dendrimers were synthesized, interest to these drug delivery systems grows every year and a great number of papers about different methods of their synthesis and behaviour in different physico-chemical conditions *in vitro* and *in vivo* were published [1]. Today the use of dendrimers in industrial and biomedical applications are wide enough [2].

Lysine dendrimers consist of natural lysine aminoacid residues (Fig. 1) [3]. Due to this reason, lysine dendrimers are usually not as toxic as other dendrimers and could be made biodegradable.

Due to the property of dendrimers to have great number of terminal groups available for functionalization, it makes possible the creation of well-characterized complexes with other compounds such as peptides.

The simulation of lysine dendrimers of different generations and their complexes was performed earlier [4]-[17].

The goal of this study is to compare process of complex formation of lysine dendrimers of 2nd and 3rd generation with two different types of therapeutic peptides (Semax and Epithalon), and to study equilibrium properties of these complexes and their destruction when external conditions were changed.

Both of the chosen peptides are regulatory therapeutic synthetic peptides. Semax is one of the few synthetic regulatory peptides that, after all the fundamental research, have found its application in therapy as a nootropic and neuroprotective agent. Its structure is shown in Table 1. Semax peptide is used for acute ischemic stroke prevention, during traumatic brain injury treatment, recovery of a patient after a stroke, in the case of optic nerve disease and glaucoma optic neuropathy.

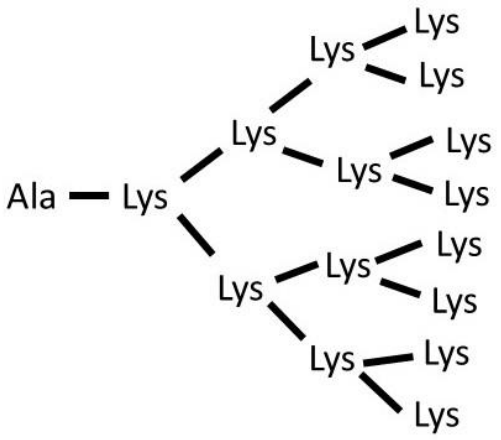

Fig. 1. Structure of a lysine dendrimer (dendron).

Epithalon is a regulatory tetrapeptide with the amino acid sequence shown in Table 1, synthesized to mimic the peptide drug "epithalamin" extracted from the pineal gland of animals. As for Epithalon, one of the most important properties of this peptide is its ability to activate the telomerase enzyme in

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patients' body and to prolong human cells life. The most well-known pharmacological properties of Epithalon are the following: regulation of the neuroendocrine system, the increase of hypothalamus sensitivity to endogenous hormonal effects, normalization of gonadotroponah hormones, uric acid and cholesterol, strengthening of the immune system, inhibition of spontaneous and induced carcinogenesis, improvement of rheological properties of blood, reduction of the formation of blood clots.

Table 1. Characteristics of peptides

Peptides	Amino acid sequence	MM, Da
Semax	MET-GLU-HIS-PHE-PRO-GLY-PRO	863
Epithalon	ALA-GLU-ASP-GLY	390

II. Methods and Materials

A. Molecular dynamics method

Molecular dynamics (MD) method is currently the main method 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:

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

It was used first in the mid-fifties of the last century 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. 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. In 1974 MD method was applied for simulation of two models of linear macromolecules: consisting of atoms connected by elastic or by rigid bonds. In 1975 the dynamics of short n-alkanes was studied.

MD is used for detailed study of many specific 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 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.

The force-field has the following form:

$$U(r_1,\ldots,r_N) = \sum \frac{a_i}{2}(l_i - l_{i0})^2 + \sum \frac{b_i}{2}(\theta_i - \theta_{i0})^2 + \\ + \sum \frac{c_i}{2}\left[1 + \cos(n\omega_i - \gamma_i)\right] + \sum 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{il}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{il}}\right)^{6}\right] + \sum k\frac{q_i q_j}{r_{ij}} \quad (2)$$

where l_i - are valence bond lengths, θ_i - valence angles values, l_{i0} and θ_{i0} - are equilibrium values of them and a_i и b_i - are force constants, correspondingly, ε_{ij} и σ_{ij} - values of Van der Waals parameters of Lenard-Jones 6-12 potential, q_i – partial charges, c_i ,γ_i and n - numerical coefficients in dihedral potential while summation is done through all i-beads or pairs of i-th and j-th beads in the system consisting of N beads.

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.

B. Model and Calculation Method

Modeling was performed using the molecular dynamics method for systems consisting of one lysine dendrimer of second generation with 16 positively charged NH_3^+ end groups, one lysine dendrimer of third generation with 32 positively charged NH_3^+ end groups, 16 Semax peptides, 16 Epithalon peptides, water molecules and chlorine 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 constructed by Avogadro molecular editor. The structures were optimized in vacuum using molecular mechanics of AMBER force field [18]. Further energy minimizations and simulations were performed using the GROMACS 4.5.6 software package [19] and AMBER_99SB-ildn force fields. The procedure of molecular dynamics simulation used in this paper for simulation of lysine dendrimers has been described earlier in [20]-[49]. In all calculations the normal conditions (temperature 300 K, pressure 1 ATM) were used.

C. Characterization of Complexes

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

$$R_g^2(t) = \frac{1}{M} \times \left[\sum_{i=1}^{N} m_i \times \left|r_i(t) - R\right|^2\right] \quad (3)$$

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 dendrimer. This function was calculated using *g_gyrate* function of GROMACS software.

To calculate the coefficient of translational mobility of dendrimer 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.

$$\left\langle \sum_t \Delta r^2(t+k\Delta t) \right\rangle = \left\langle \sum_t (r(t+k\Delta t) - r(t))^2 \right\rangle = 6Dt \quad (4)$$

III. Results and Discussion

To check if lysine dendrimer forms a complex with Semax and Epithalon peptides we prepared systems containing of lysine dendrimer of the 2nd generation and 3rd generation, 16 Semax peptides, 16 Epithalon peptides and counterions in water and studied the time evolution of these systems.

Snapshots of systems consisting of dendrimer, Semax or Epithalon peptides, ions and water during simulation are shown on Fig. 2 (water molecules are not shown for clarity). It is clearly seen that at the beginning of process in cases of 16 Semax and 16 Epithalon (Fig. 2, a, d) peptide molecules are rather far from a 2nd generation dendrimer. After 30 ns (Fig. 2, b, e) some part of peptide molecules are already adsorbed on the surface of dendrimer, and in the end after 160 ns (Fig. 2, c, f) all peptide molecules in the systems are on its surface.

Atoms of dendrimer molecule are shown as beads with diameter equal to their van der Waals radii. Valence bonds of various peptides are shown with lines of different colours (backbone of each peptide is shown by thick line of the same colour as valence bonds).

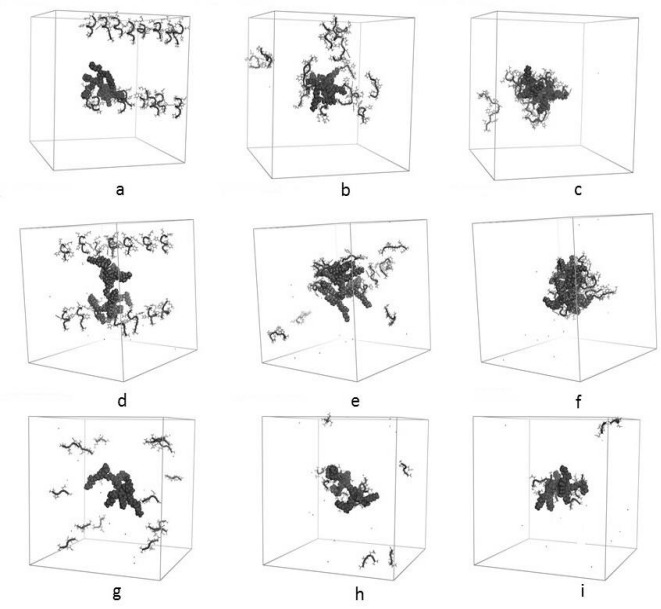

Fig. 2. Snapshots of the G2 dendrimer with Semax peptides at different time moments t = 0 (a); t = 20 ns (b); t = 160 ns (c); G3 dendrimer with 16 Semax peptides at different time moments t = 0 (d); t = 20 ns (e); t = 160 ns (f); G2 dendrimer with Epithalon peptides at different time moments t = 0 (g); t = 20 ns (h); t = 160 ns (i)

A. *Dendrimer-Peptides Complex Formation.*

The time dependence of gyration radius R_g at the beginning of calculation describes the process of equilibrium establishment during complex formation (Fig. 3). Complex of G3 dendrimer and 16 Semax forms only after 40 ns.

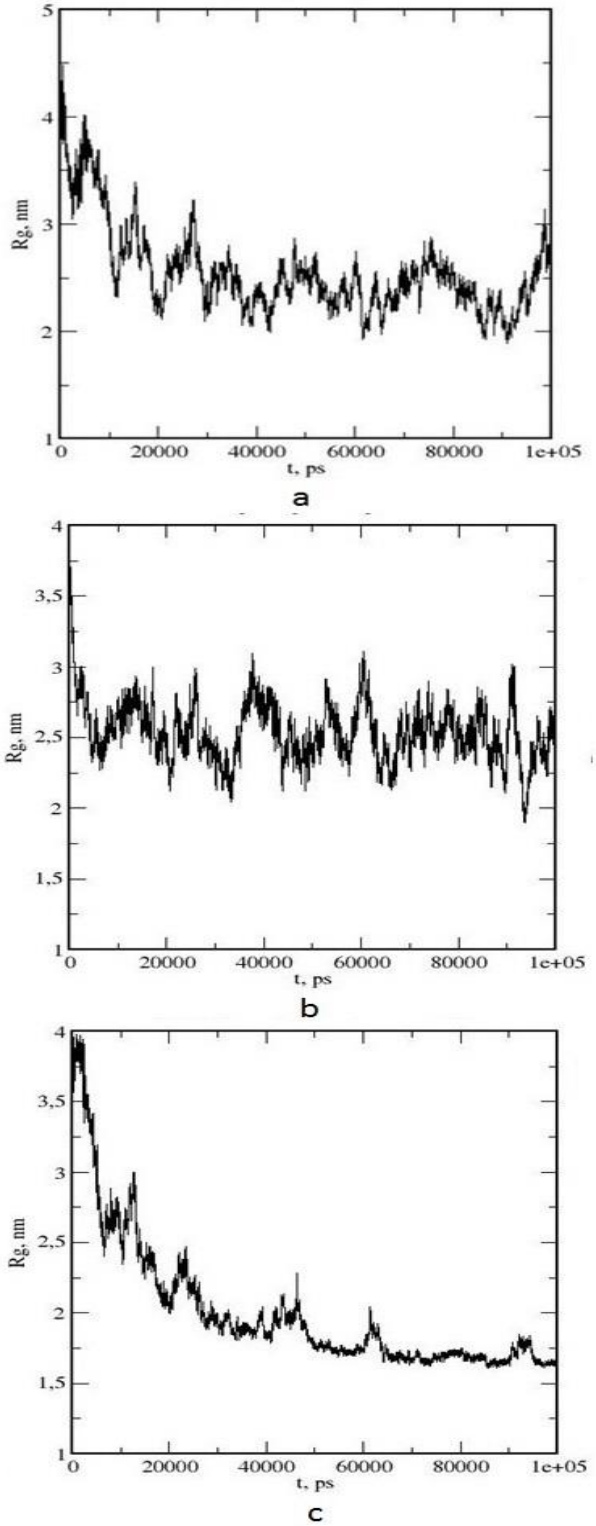

Fig. 3. System of dendrimer G2 and 16 Semax peptides (a); of dendrimer G2 and 16 Epithalon peptides (b); of dendrimer G3 and 16 Semax peptides (c)

From Fig. 3 it can be seen that complex with G2 dendrimer and 16 Epithalon forms within 20 ns. Complex of G2 dendrimer and 16 Semax forms twice longer. It's quite natural since Epithalon peptides are twice shorter than Semax and has twice more opposite charges. After that the complexes sizes R_g

fluctuate slightly, but their average value practically does not change with time. Therefore, we can assume that the systems are in equilibrium state.

Similar information could be obtained from time dependence of distance between dendrimer and peptides (see Fig. 4). At times less than 40 ns peptides become attracted by oppositely charged dendrimer and distance between dendrimer and peptides decrease in both cases. After that the distance does not change further with time. It means that we obtained equilibrium dendrimer-peptides complex at time $t > 20$ ns for G2 and 16 Epithalon peptides and at time $t > 40$ ns for G2 and 16 Semax peptides.

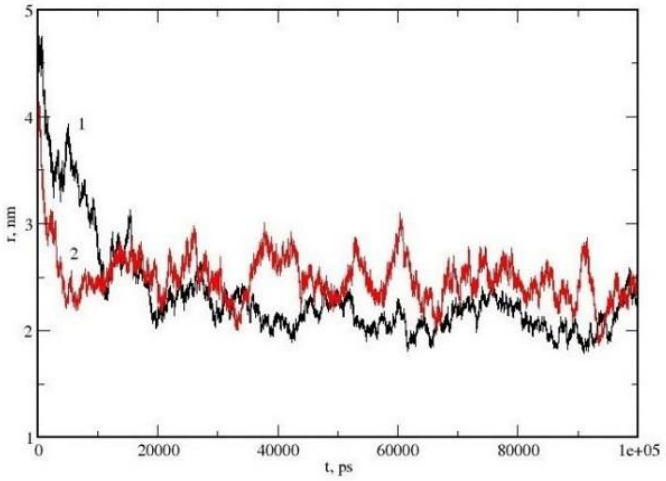

Fig. 4. Changes in distances between peptides and dendrimer: 1 – G2 and 16 Semax; 2 – G2 and 16 Epithalon

The total number of hydrogen bonds (N) between dendrimer and peptides can characterize complex formation. The dependence of this value on time is shown on Fig. 5 and demonstrates how the number of contacts between dendrimer and peptides increases complex formation. In the beginning of simulation there are no contacts between dendrimer and peptides and hydrogen bond number between them equal zero. The first system (Fig. 5, a) reaches equilibrium (plateau) after 40 ns. The second system (Fig. 5, b) reaches equilibrium twice earlier. The third system (Fig. 5, c) reaches equilibrium after 40 ns.

It correlates with the results of the inertia radii balance obtained in Fig. 3 and Fig. 4.

This value was calculated using g_hbonds function from package of GROMACS. The average number of hydrogen bonds was equal to 19 for G2+16 Semax, equal to 39 for G3+16 Semax and equal to 20 for G2+16 Epithalon.

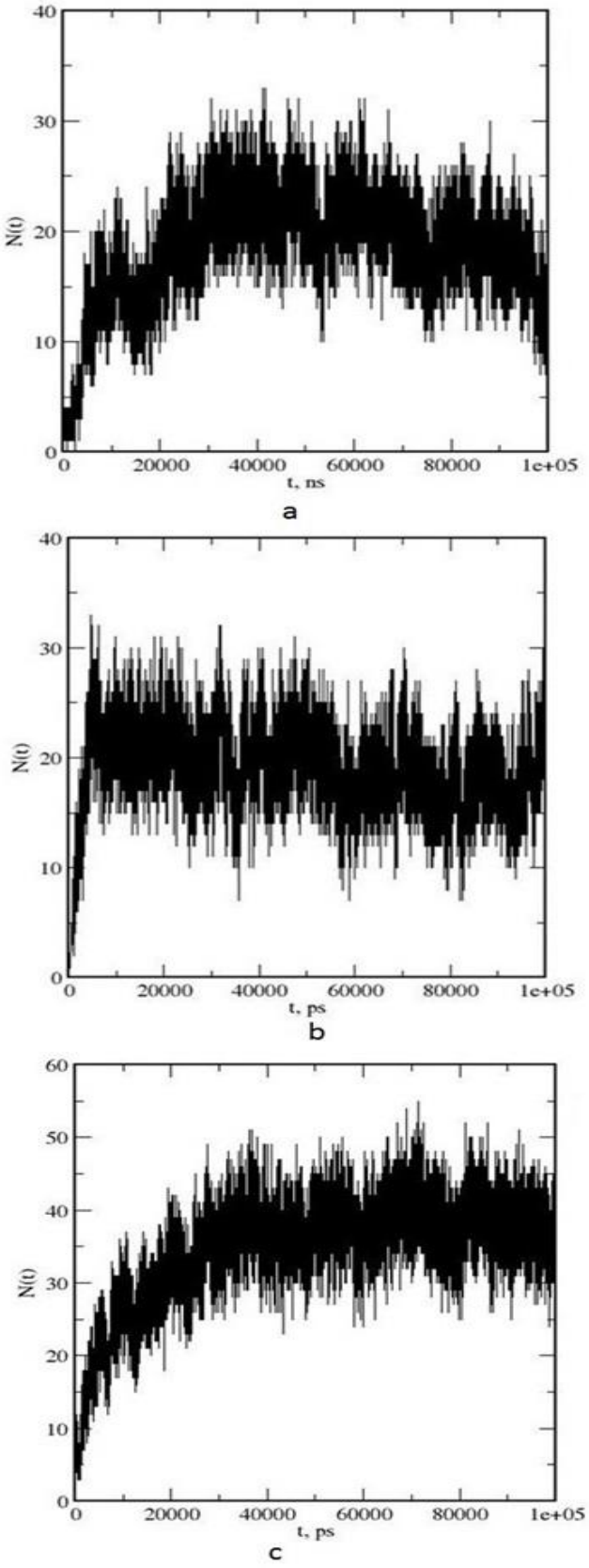

Fig. 5. Time dependence of dendrimer-peptides hydrogen bond number (N) during dendrimer-peptides complex formation: 1 – G2 and 16 Semax; 2 – G2 and 16 Epithalon; 3 – G3 and 16 Semax

B. Modelling of equillibrium state of dendrimer-peptide complexes

The mean square radius of gyration Rg of the dendrimers (G2 and G3) and three complexes (G2 and 16 Semax peptides, G3 and 16 Semax peptides, G2 and 16 Epithalon peptides) was calculated. It was obtained that the value of Rg of the complex of G2 and 16 Semax was nearly twice larger than the size of a dendrimer itself (see Tab.2). The same result was obtained for the complex of G2 and 16 Epithalon. In case of G3 and 16 Semax the size of a complex was only 1.15 times larger than the size of a dendrimer. The shape of all three 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. 2. For example, in the simplest case, anisotropy can be characterized by ratio R_g^{33} / R_g^{11}.

Table 2. Eigenvalues R_g^{11}, R_g^{22}, R_g^{33} of tensor of inertia in dendrimer and dendrimer - peptide complex

System	Rg^{11}, nm	Rg^{22}, nm	Rg^{33}, nm	Rg, nm	Rg^{33}/Rg^{11}
G2	0.64	0.97	1.08	1.12	1.69
G2+16 Semax	1.36	1.88	1.97	2.30	1.46
G3	0.98	1.22	1.32	1.44	1.34
G3+16 Semax	1.24	1.34	1.51	1.66	1.22
G2+16 Epithalon	1.76	2.08	2.26	2.44	1.28

The largest component of inertia tensor Rg^{33} of complex with G3 and 16 Semax peptides is 0.76 times smaller than this component in complex with G2 and 16 Semax peptides. At the same time, the smallest component Rg^{11} of the complex with G3 and 16 Semax peptides is just in 0.91 times smaller than that component in complex with G2 and 16 Semax peptides.

The largest component of inertia tensor Rg^{33} of complex with G2 and 16 Semax peptides is 0.87 times smaller than this component in complex with G2 and 16 Epithalon peptides. At the same time, the smallest component Rg^{11} of the complex with G2 and 16 Semax peptides is just in 0.77 times larger than that component in complex with G2 and 16 Epithalon peptides.

The distribution function $p(R_g)$ of gyration radius R_g gives more detailed information about fluctuations of R_g of dendrimers-peptides complexes. This function is shown in Fig. 6.

The distribution of R_g in complex with G2 and 16 Semax and Epithalon peptides have broader $p(R_g)$ function than G3 and 16 Semax. It means that fluctuation of size in these systems are greater and peptides are probably adsorbed on dendrimer not so strong as in system with G3 and 16 Semax peptides.

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. 7).

$$p(r) = \frac{m_{comp\,(r)}}{V_{comp\,(r)}} \qquad (5)$$

where m_{comp} – mass of all atoms in complexes; V_{comp} – volume of complexes.

The data demonstrates that in all cases dendrimers (curve 2) are located in the center of the complex and peptides (curve 1) are mainly on the surface of complex. At the same time, some fraction of peptides could slightly penetrate into outer part of dendrimer.

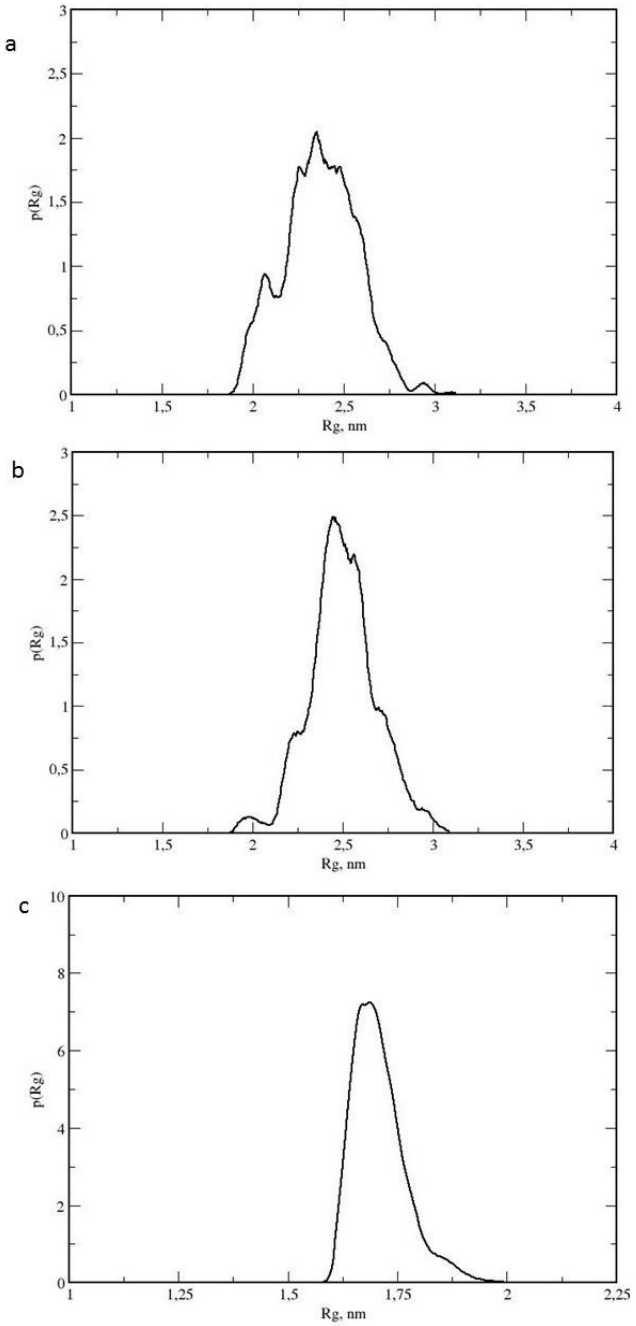

Fig. 6. Distribution function p(Rg) of gyration radius Rg: a – G2 and 16 Semax, b – G2 and 16 Epithalon; c – G3 and 16 Semax

The distribution function of hydrogen bonds number (Fig. 8) 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 (19, 39 and 20) and thus are quite symmetrical. Fluctuations in hydrogen bonds number for the system with G2 and 16 Semax peptides are in the range of 8-30, for the system with G2 and 16 Epithalon peptides are in the range of 9-29, for the system with G3 and 16 Semax peptides are in the range of 25-50.

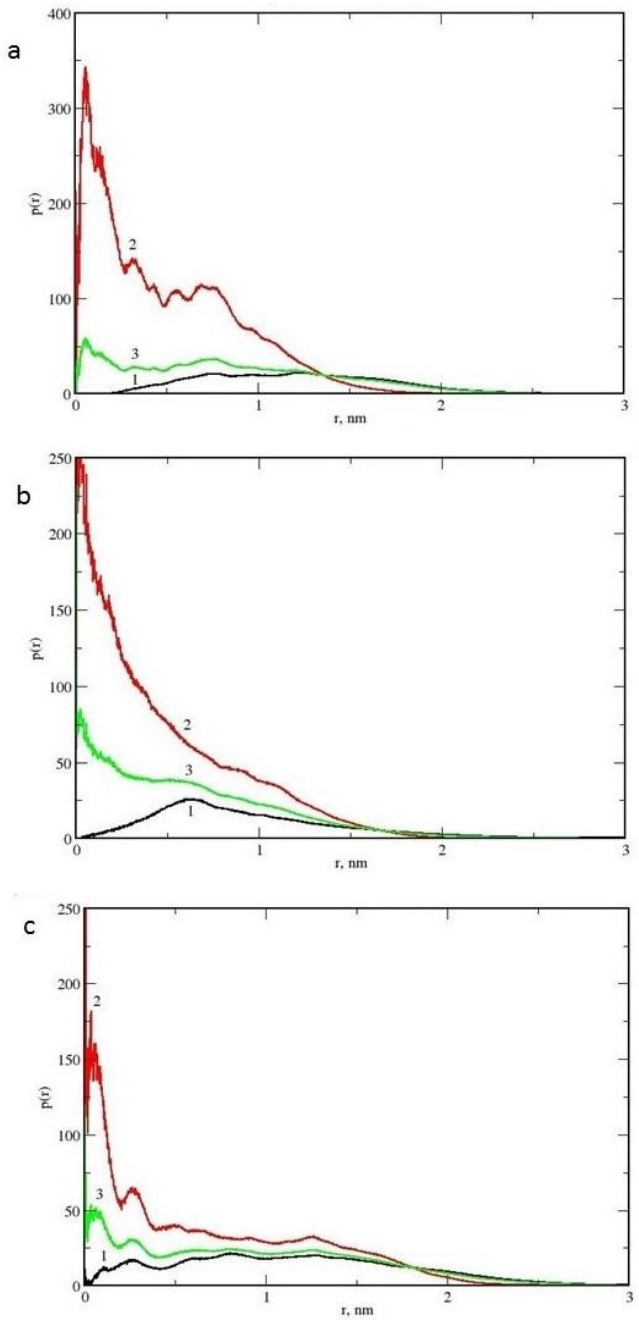

Fig. 7. Radial distribution p(r) density of complexes G2 and 16 Semax (a); G2 and 16 Epithalon (b); G3 and 16 Semax (c). Distribution curves: peptide atoms (1); dendrimer atoms (2); all atoms of complex (3)

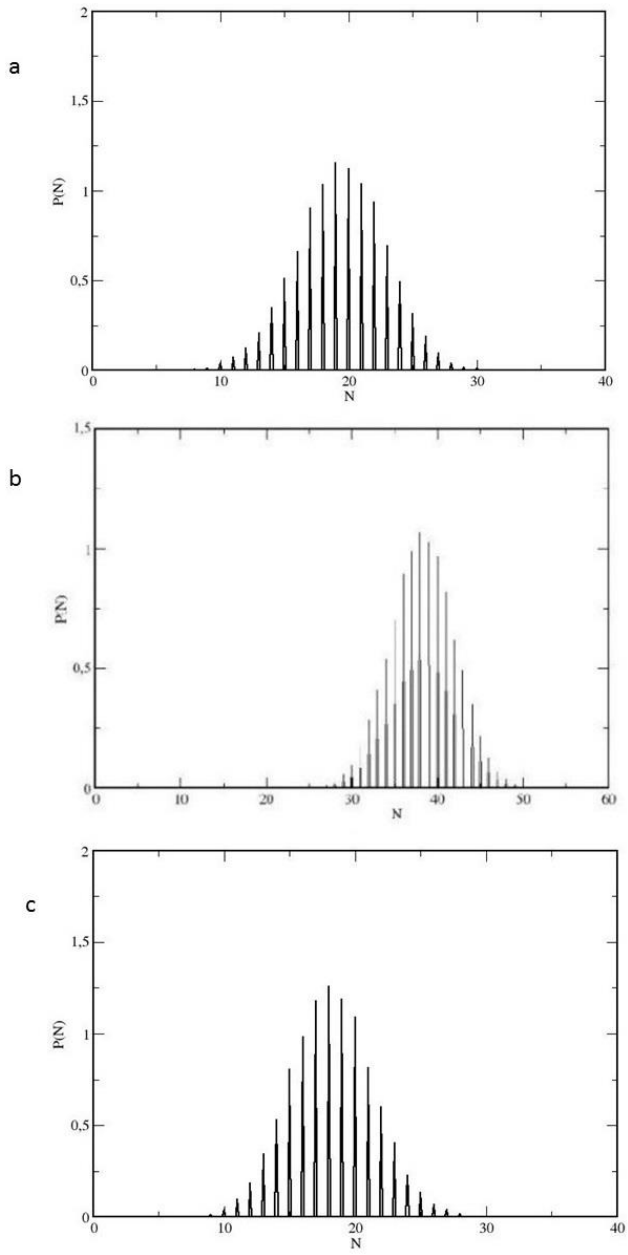

Fig. 8. The distribution function P(N) of hydrogen bonds number N of complexes: complex G2 and 16 Semax (a); complex G3 and 16 Semax (b); complex G2 and 16 Epithalon (c)

The other characteristic of interaction between dendrimer and peptides (1) in equilibrium dendrimer-peptide complex is the distribution of ion pairs number between their oppositely charged groups. Fig. 9 shows the dependence of ion pairs number on the corresponding distance between pairs of charges of dendrimer and peptides in our complex.

It is seen that there is very sharp peak in all cases, at the distance corresponding to the direct contact between positively charged groups (NH_3^+) of dendrimer and negatively charged groups (COO^-) of the glutamic acid in peptides (Fig 9, curves 1). At the same time, NH_3^+ groups of dendrimer form much fewer ion pairs with ions (Fig 9, curves 2).

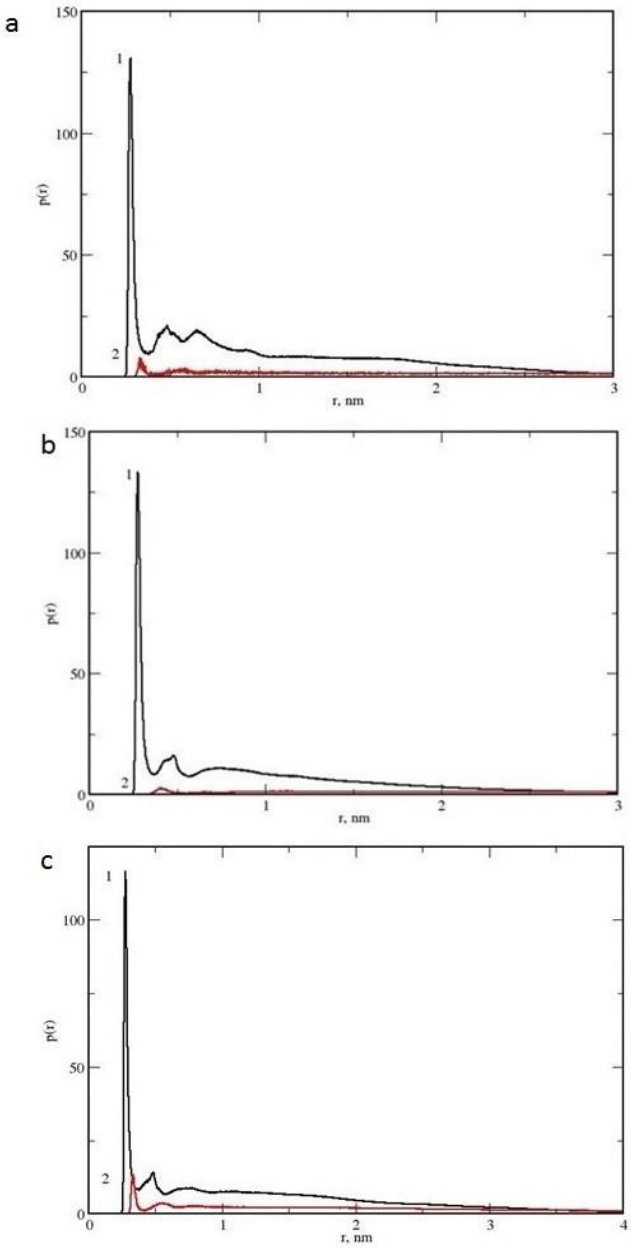

Fig. 9. Function of ion pairs radial distribution: a – G2 and 16 Semax, b - G2 and 16 Epithalon, c - G3 and 16 Semax. Curves: 1 - NH_3^+ groups of dendrimer and COO^- groups of peptides; 2 - NH_3^+ groups of dendrimer and ions

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. 10). MSD was calculated using g_msd function of GROMACS. Coefficient of translational diffusion of the complex of G2 with 16 Semax was obtained from the slope of this time dependence and was equal to $(0.12 \pm 0.03) \times 10^5$ sm^2/s. For complex of G3 with 16 Semax it was equal to $(0.10 \pm 0.05) \times 10^5$ sm^2/s. Coefficient of translational diffusion of the complex with Epithalon was also obtained from the slope of this time dependence and was equal to $(0.21 \pm 0.03) \times 10^5$ sm^2/s. It was greater than for dendrimers with Semax peptides due to smaller size of Epithalon peptides.

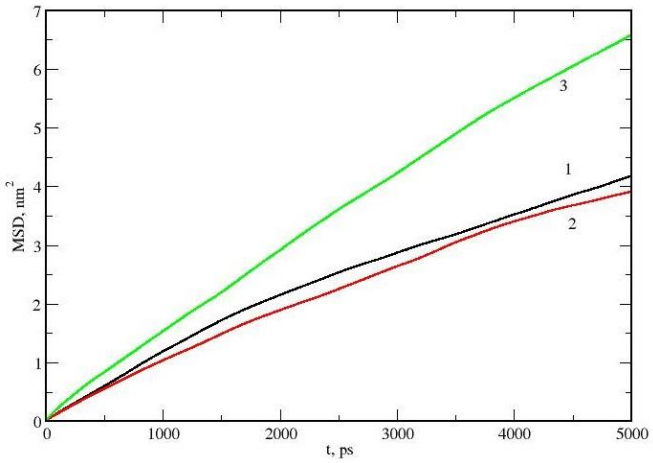

Fig. 10. Mean square displacements of the centres of inertia: complex of G2 and 16 Semax (1); G3 and 16 Semax (2); G2 and 16 Epithalon (3)

C. Modelling of the Disruption of Dendrimer-peptide Complexes

A change in the properties of the medium, for example, pH, can lead to a significant decrease, and even complete nullification of the positive charge of the dendrimer. Here the behaviour of the previously studied dendrimer complexes of the 2nd and 3rd generation dendrimers with 16 Semax peptides is simulated after the complete switching off all positive dendrimer charges.

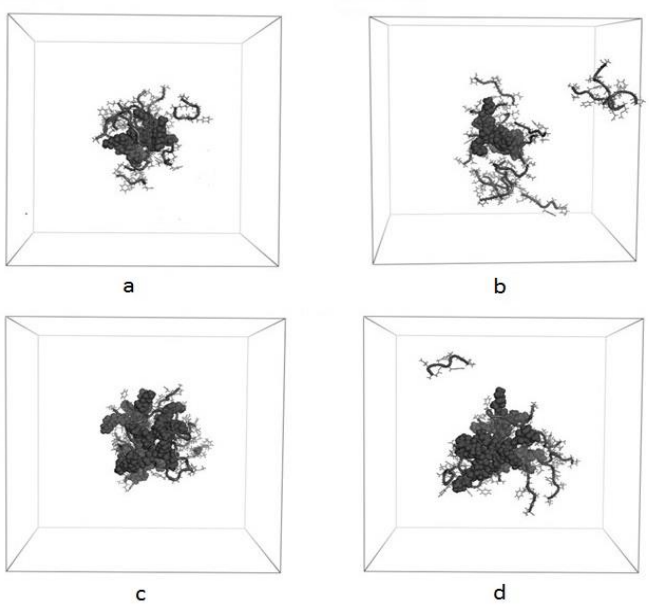

Fig. 11. Snapshots of the G2 (a, b) and G3 (c, d) dendrimers with 16 Semax peptides at different time moments *t* before and after switching off charges of dendrimers

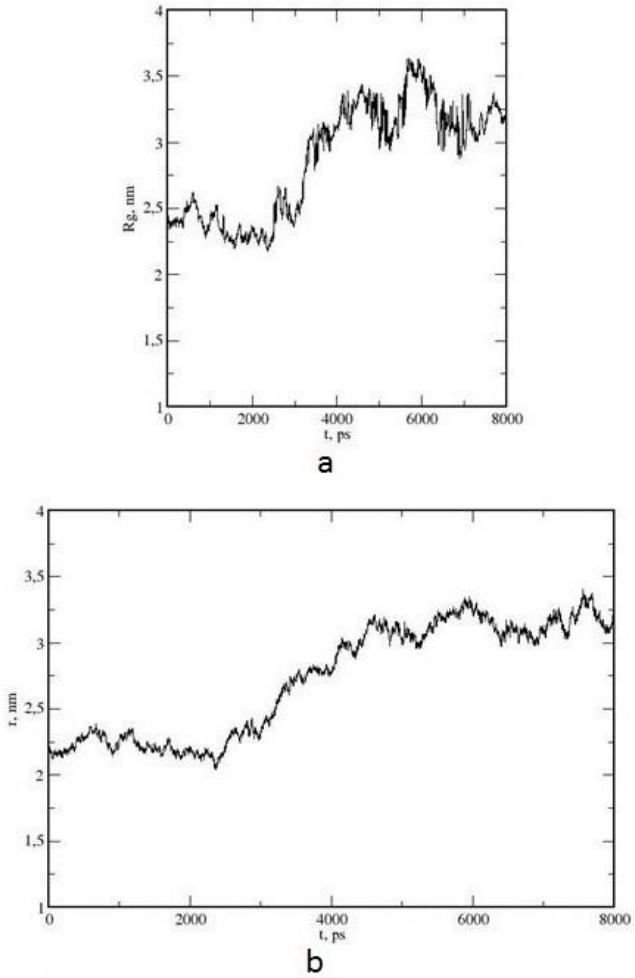

Fig. 12. Dependence of size *Rg* of complexes of dendrimers G2 (a) with 16 Semax; the distance *r* between the centers of the G2 (b) dendrimers and peptides on the time *t* after switching of charges of dendrimer.

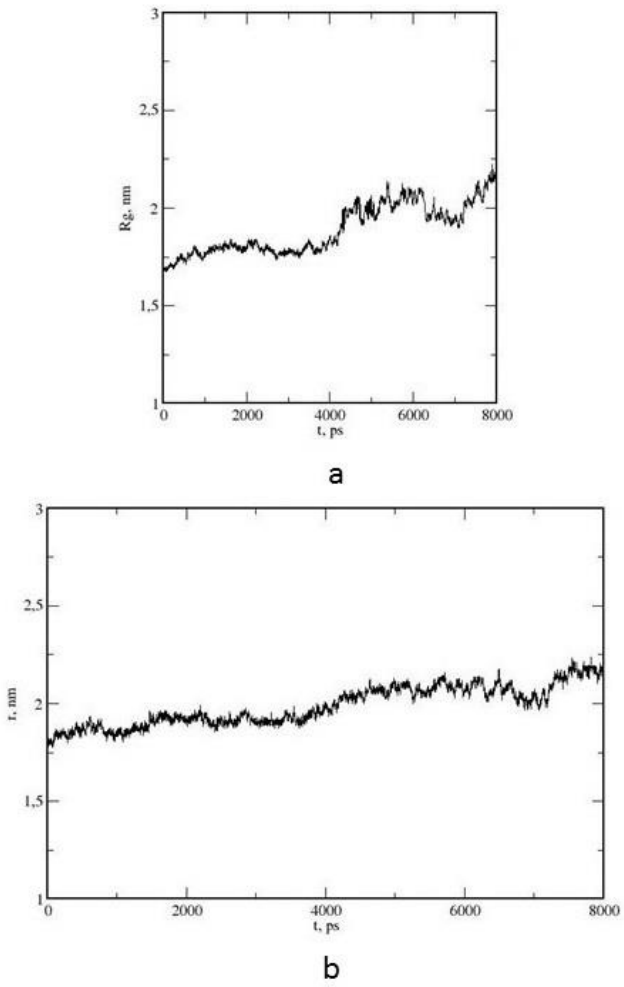

Fig. 13 Dependence of size *Rg* of complexes of dendrimers G3 (a) with 16 Semax; the distance *r* between the centers of the G3 (b) dendrimers and peptides on the time *t* after switching of charges of dendrimer.

Instantaneous snapshots of dendrimer were taken, before and after switching off dendrimer charges (Fig. 11). It is clearly seen from these figures that at the beginning of the calculation (Fig.11a) all peptide molecules are on or very near the surface of the dendrimer in both cases. After 5 ns (Fig.11b), some of the peptide molecules have already left the surface of the dendrimers. However, the destruction of the complex occurs rather slow (see increase of Rg of complex and distance between dendrimers and peptides after switching off charges of dendrimer in Fig.12 and Fig. 13) due to the remaining hydrophobic interactions between the atoms of the dendrimer and the peptides.

IV. Conclusion

The process of complexes formation by lysine dendrimers of second and third generation and therapeutic model peptides (Semax and Epithalon), the equilibrium structures of these complexes and its destruction under pH changes were investigated by the method of molecular dynamics simulation. It was shown that formation of dendrimer-peptide complexes occurs very quickly in all cases. It was obtained that complex of G2 dendrimer and 16 Semax forms twice longer than complex of G2 and 16 Epithalon. It was explained by differences in peptides' structure – Epithalon is smaller and has more opposite charges than Semax.

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 dendrimer atoms are mainly inside the complex, while most of peptide atoms are on its surface.

It was demonstrated, that in all cases there is a direct contact between positively charged groups (NH_3^+) of dendrimer and negatively charged groups (COO^-) of the

glutamic acid in Semax peptides and of the glutamic acid and asparagine in Epithalon peptides.

It was demonstrated that there are strong electrostatic interactions between dendrimer and peptides in all complexes.

Switching off these interactions (for example, by pH changes) leads to the destruction of the complexes and the release of peptides from it. The destruction is not very quick due to the remaining hydrophobic interactions between the atoms of the dendrimer and the peptides.

These complexes can be used in future for oral delivery of different therapeutic peptides to brain and other parts of the body in treatment of cancer, brain diseases and etc.

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