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ORIGINAL PAPER

Effect of the aminoacid composition of model α-helical peptides on the physical properties of lipid bilayers and peptide conformation: a molecular dynamics simulation

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Abstract The interaction of a model Lys flanked α-helical peptides K_2-X_{24}-K_2, (X = A,I,L,L+A,V) with lipid bilayers composed of dimyristoylphosphatidylcholine (DMPC) and dipalmitoylphosphatidylcholine (DPPC) both, in a gel and in a liquid-crystalline state, has been studied by molecular dynamics simulations. It has been shown that these peptides cause disordering of the lipid bilayer in the gel state but only small changes have been monitored in a liquid-crystalline state. The peptides affect ordering of the surrounding lipids depending on the helix stability which is determined by amino acid side chains – their volume, shape, etc. We have shown that the helix does not keep the linear shape in all simulations but often bends or breaks. During some simulations with a very small difference between hydrophobic length of peptide and membrane thickness the peptide exhibits negligible tilt. At the same time changes in peptide conformations during simulations resulted in appearance of *superhelix*.

Keywords Bilayer lipid membranes · Helical peptides · Molecular dynamics simulations · Phase transitions

Introduction

Lipid-protein interactions are of fundamental importance for understanding both structural integrity and functions of biological membranes. Among membrane proteins, the integral ones are of special importance due to the wide variety of the function they perform in the cells, such are for example the receptor activity, energy transduction or active transport. Despite extensive experimental and theoretical studies, the knowledge of the mechanisms of protein-lipid interaction is still incomplete (see [1–3] for recent reviews). In order to overcome the problems connected with a complicated structure of integral proteins, their isolation and purification, chemically synthesized peptides that model of specific regions of natural membrane proteins have been used in biophysical studies. Among others, the α-helical peptide acetyl-K_2-L_{24}-K_2-amide (L_{24}), has been designed [4]. This peptide contains a long sequence of hydrophobic leucine residues flanked at both N- and C-termini with two positively charged, polar lysine residues. The central polyleucine region of this peptide was considered to form a maximally stable α-helix in the hydrophobic environment of the lipid core, while the dilysine caps anchoring the ends of these peptides to the polar surface of the bilayer lipid membrane (BLM) and inhibiting the peptide lateral aggregation.

Detailed biophysical studies of the interaction of P_{24} or L_{24} [4, 5] or similar Trp flanked peptides [6] with BLM suggested that their incorporation into phosphatidylcholine bilayers resulted in the decrease of the ordering of the bilayer in a gel state and in this increasing in a liquid crystalline (LC) state. Our studies performed by means of precise densitometry and ultrasound velocimetry methods [7] showed that L_{24} peptide induced complex effect on lipid bilayers of various thickness. Detailed analysis of the interaction of acetyl-K_2-L_m-A_n-K_2-amide (m+n=24) with phospholipid bilayers suggests, that stable transmembrane peptide association depends on the Leu/Ala ratio [8]. Further information on the structure and dynamics of lipid bilayer as well as on the molecular mechanisms of protein-lipid interactions, can be obtained by the method of molecular dynamics simulations, which are widely used for the study mechanisms of protein-lipid interactions [1, 9–14]. In this study we have applied the molecular dynamics

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simulations on the model helical peptides composed of A_{24}, L_{24}, $(LA)_{12}$, I_{24}, P_{24} and V_{24} incorporated into the phospholipid bilayers (DMPC, DPPC) and analyzed their effect on physical properties of the membranes both in the gel and in the liquid-crystalline state.

Methods

MD has been applied for the determination of changes of physical properties of lipid bilayers caused by the incorporated peptide as well as for the determination of possible peptide structural alterations. MD were performed under periodic boundary conditions using the Gromacs software [15] and the Gromos87 [16] forcefield with corrections for lipids [17, 18]. The initial models of transmembrane α-helix peptides have been generated by means of HyperChem [19]. Preequilibrated DMPC and DPPC bilayers with 128 lipid molecules and 3655 molecules of water in L_α liquid-crystal state published by Tieleman et al. [20] have been used in bilayer modeling. For the simulations with membrane in L_β' gel state, the bilayers were created on the basis of the experimental data (e.g., taking into account area per lipid and bilayer thickness) [3, 21]. Initial structures were solvated with SPC water (4764 molecules for DMPC and 4784 for DPPC), energetically minimized and simulated for over 20 ns until the membrane parameters were close to the experimental values. A cylindrical hole has been created in the center of a bilayer by removing four lipids whose atoms were within 0.23 nm of the central axis of a cylinder. The peptide was then inserted into the cavity. The resulting system (peptide, 124 PC molecules, four chlorine ions and water) consisted from more than 16,000 atoms for LC and more than 20,000 for gel state of membrane. The system has been energetically minimized and equilibrated during 0.5 ns while the peptide's atoms were fixed. Then MD took place for at least 40 ns at temperatures T=288 K and 310 K (bellow and over phase transition) for DMPC and 296 K / 346 K for DPPC bilayer. MD was performed with constant pressure of 1 bar (semi-isotropic barostat), constant temperatures and with the time step of 2 fs. The LINCS algorithm has been used to constrain covalent bond lengths. The used conditions were similar to that reported by Berger et al. [22].

Trajectories were analyzed from the last 5 ns of the simulations by subroutines (programs) available from Gromacs package.

Results and discussion

Interactions of the peptides with lipid bilayers have been studied in a gel and in a liquid-crystalline state. At the end of the simulation the hydrophobic length of unmodified bilayers in a gel state had the value of 3.60–3.62 nm for DPPC and 3.26–3.27 nm for DMPC. The area per lipid was 0.4733 nm^2/DPPC and 0.4676 nm^2/DMPC membrane, respectively. The corresponding values for lipid bilayers in a LC state indicated in Tieleman's web site are as follows. The hydrophobic thickness of bilayers was 2.97 nm for DPPC and 2.77 nm for DMPC, respectively. The values of area per lipid parameter were 0.629 nm^2/DPPC and 0.596 nm^2/DMPC, respectively.

Based on molecular modeling studies, it has been estimated, that the hydrophobic length of the α-helix composed of 24 Leu residues is approx. 3.1 nm [4] (note that this is lower in comparison with routinely calculated end-to-end

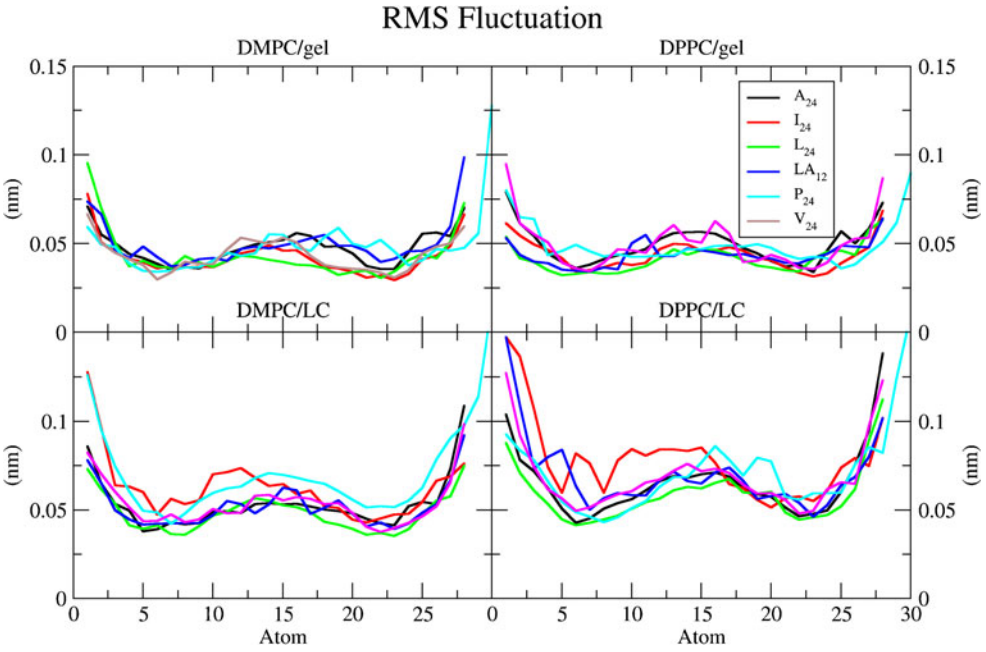

Fig. 1 RMS fluctuations from last 5 ns. Each peptide has lower stable parts at both ends and in the middle. Stability of peptide is influenced by sidechains – Leu stabilizes helix, Ala, Ile and Val increase the fluctuations

distance of this α-helical peptide assuming 0.15 nm projection on a z-axis per amino acid residue [23]). This is shorter than hydrophobic thickness of the bilayer in a gel state (3.44 for DPPC and 3.2 nm for DMPC), but longer for BLM in a liquid-crystalline state (2.85 nm for DPPC and 2.62 nm for DMPC) [5]. Therefore we have analyzed the geometry of the systems in both gel and LC phases.

Simulations of lipids in the corresponding phase differ only in amino acid side chains of embedded peptide. The different length and the branching of the side chains affect the α-helix stability. The most stable helix is produced from poly-Leu core (branching on C^{γ} atom) – L_{24} and P_{24}. I_{24} and V_{24} are branched on C^{β} and therefore they are less stable [23]. These residues prefer β-strand conformation. A_{24} has small, not branched and less hydrophobic side chains (poly-Ala peptide prefers head group environment parallel to the membrane surface) and is preferable in α-helix conformation. $(LA)_{12}$ is composed of Leu and Ala residues and exhibits properties that are between that of L_{24} and A_{24}. This side chain effect can be seen during simulations on RMS fluctuation graphs (Fig. 1). In general, the highest fluctuations took place at the polar part and in the central, hydrophobic core of the membrane. The later part is of lower density. In all simulations I_{24} and V_{24} are of lowest stability (I_{24} is even less stable). In contrast the L_{24} peptide is the most stable. The fluctuations of $(LA)_{12}$ and P_{24} in the gel phase are more remarkable. The changes of the configuration and twist of the helix structure due to these fluctuations resulted in the appearance of *superhelix* (like in DNA or *coiled coil loop* in leucine zipper – but only one helix is present). This *superhelix* is validated by structure visualization shown in Fig. 2.

To eliminate differences between the peptide length and membrane thickness, the peptide tilts in most cases. However the tilt angle (see Table 1) is not equal for all systems studied. There are five peptide-membrane systems for which the tilt exhibits minimal value and creates superhelical structure: $(LA)_{12}$ in DPPC/gel and DMPC/gel; P_{24} in DPPC/gel; V_{24} in DMPC/gel. This includes also L_{24} in DPPC/gel, but simulation breaks the helix approximately one turn from C end. In all these simulations a small tilt of peptide is produced. In other simulations the peptide bends or breaks the helical structure – mostly when peptide is composed from poly-Ala core. If the peptide has poly-Leu core it keeps straight helix conformation. From the tilt angle and the length of the peptide the effective thickness of peptide can be calculated. It is also possible to calculate thickness of the membrane (Table 1). Membrane is thicker only in those five cases mentioned above. In the final stage of simulations the peptide is tilted a little more in order to compensate the differences in thickness ($\leq$ 0.1 nm). The final difference between the thickness of 1^{st} lipid shell and peptide is always smaller than 0.5 nm. Such difference can compensate Lys residues by reorienting their side chains.

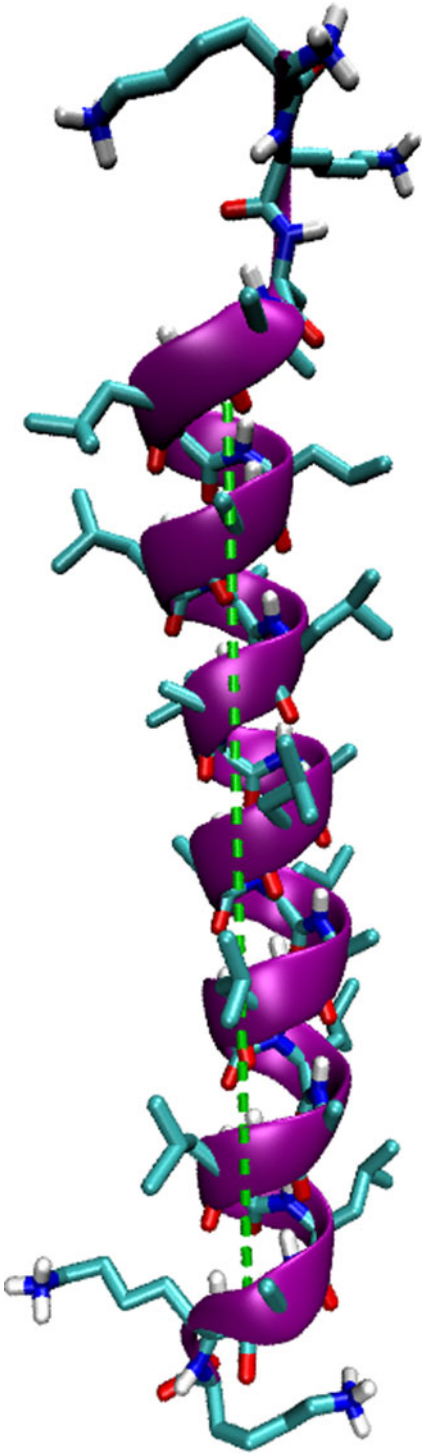

Fig. 2 Superhelix configuration on P_{24} peptide at the end of the simulation. Lime dashed line is axis that connects centers on the beginning and ends of peptide. The peptide tilts around this axis

The changes of other peptide parameters (rise per residue, radius of helix, Φ and Ψ angles, twist per residue, etc.) are negligible. Φ and Ψ angles remain stable. The only significant changes are in parts of the peptide, where it bends or breaks.

Table 1 Angles and lenghts of hydrophobic parts - membrane and peptide

System	Angle 1st & 2nd half [nm]	Tilt [°]	Peptid effective thickness [nm]	Full peptide's length [nm]	Membrane effective thickness 1st shell [nm]	Membrane effective thickness 2nd shell [nm]
A_{24}/DMPC/gel	9.33	35.55	2.75	3.38	3.00	2.83
A_{24}/DPPC/gel	6.88	13.9	3.29	3.39	3.33	3.40
A_{24}/DMPC/LC	7.16	50.85	2.15	3.41	2.07	2.34
A_{24}/DPPC/LC	7.16	37.73	2.69	3.41	2.71	2.71
I_{24}/DMPC/gel	4.11	22.43	3.25	3.52	3.08	2.97
I_{24}/DPPC/gel	8.29	18.13	3.31	3.49	3.29	3.33
I_{24}/DMPC/LC	18.46	47.49	2.4	3.56	2.43	2.52
I_{24}/DPPC/LC	8.74	9.19	3.55	3.6	3.06	2.9
L_{24}/DMPC/gel	5.24	37.98	2.67	3.39	2.66	2.74
L_{24}/DPPC/gel	12.66	7.34	3.4	3.43	3.26	3.49
L_{24}/DMPC/LC	10.5	51.92	2.12	3.44	2.4	2.55
L_{24}/DPPC/LC	9.19	43.63	2.49	3.43	2.59	2.72
$(LA)_{12}$/DMPC/gel	14.65	16.17	3.26	3.4	2.82	2.93
$(LA)_{12}$/DPPC/gel	13.16	5.61	3.38	3.39	3.37	3.43
$(LA)_{12}$/DMPC/LC	8.91	50.43	2.18	3.42	2.36	2.27
$(LA)_{12}$/DPPC/LC	6.68	41.19	2.58	3.43	2.53	2.74
P_{24}/DMPC/gel	10.42	13.32	3.45	3.54	2.93	2.92
P_{24}/DPPC/gel	5.97	15.69	3.29	3.42	3.4	3.55
P_{24}/DMPC/LC	5.48	50.72	2.28	3.59	2.48	2.56
P_{24}/DPPC/LC	6.12	51.56	2.15	3.45	2.63	2.66
V_{24}/DMPC/gel	19.63	5.24	3.39	3.41	3.24	3.1
V_{24}/DPPC/gel	7.21	3.56	3.48	3.49	3.14	3.05
V_{24}/DMPC/LC	4.86	47.33	2.36	3.48	2.49	2.49
V_{24}/DPPC/LC	7.24	46.66	2.4	3.5	2.58	2.76

The properties of lipids surrounding the peptide also change. They can be separated into three shells. First shell is formed by lipids in a close proximity of peptide (in a distance up to the 0.8 nm from peptide), 2nd shell is formed by lipids in a distance between 0.8 and 1.6 nm and the 3rd shell is at distance > 1.6 nm from the peptide surface. Lipids behind 2nd shell are nearly not affected by the presence of the peptide [11]. As can be seen in Table 1, the thickness of the membrane is changed. In most of the simulations the peptide tilts more than needed if taking into account the differences between peptide length and membrane thickness. Therefore the effective length of the peptide is shorter than bulk membrane thickness and the peptide surrounding lipids are shorter (first lipid shell is thinner; the thickness of second shell is closer to that of the thickness of bulk lipid bilayer). Because membrane related processes are relatively slow it is possible that peptides overshot the right tilt and they would came back after a certain time to match thickness of membrane.

We also analyzed the deuterium order parameters, the amount of dihedral angles in *trans* conformation and the number of transitions between *trans* and *gauche* conformations. All of these parameters are calculated for both 1st and 2nd shells.

The changes of the order parameters are shown on the Fig. 3. For membranes in a gel state the peptide causes disordering of the membrane, i.e., the order parameters of the first shell decrease. In the case of LC phase, nearly all simulations produce only small changes in ordering except A_{24} and I_{24}. I_{24} is broken in the middle which resulted in the decrease of the order in this region. The order parameters for L_{24} or P_{24} peptides are comparable with that reported by Tieleman et al. [11] and those obtained in experiments [4–6]. There is unfortunately not sufficient information for comparison of the behavior of other peptides.

The differences between the peptides are caused by more or less fluctuating peptide backbone depending on amino acids side chains. More fluctuating peptide pushes surrounding lipids away. These changes result in an increase of local density and the lipids must change their conformation to possess less kinks and to decrease area per lipid.

The amount of the dihedral angles in the trans conformation (see Table 2) depends on the temperature and phase of a membrane – the lower value was typical for LC (72–76 %) and higher for the gel state (87–90 %) of unmodified membranes. In the presence of the peptide the amount of trans dihedral angles decreases in gel state and increases in LC

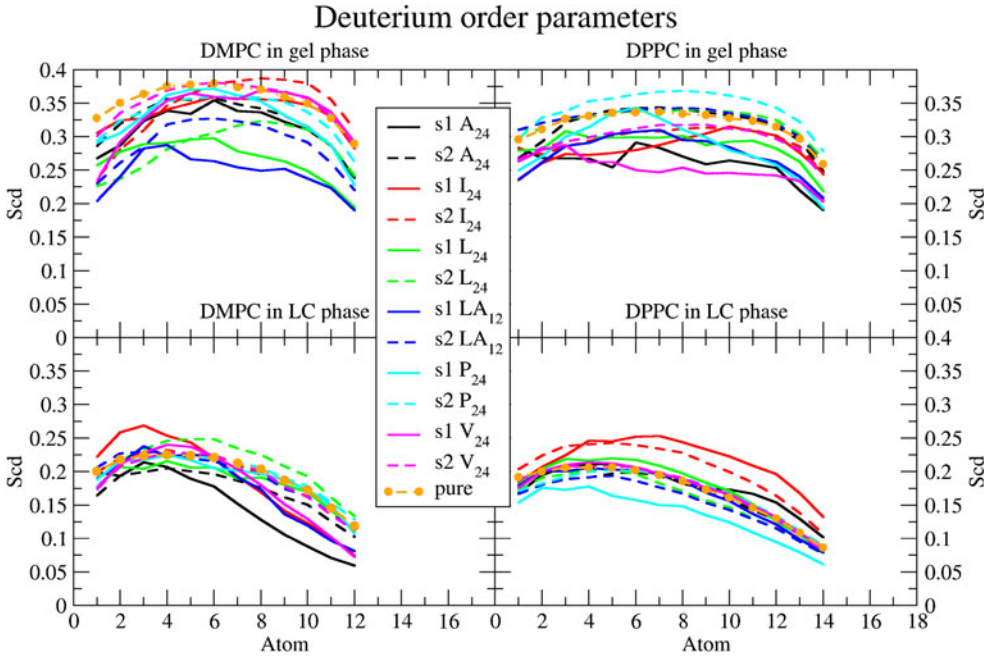

Fig. 3 Order parameters from last 5 ns of the simulations of peptides and four types of lipid bilayers. Lipids are separated into two shells around peptide: nearer to the peptide and more influenced as *s1* and farther, less influenced, as *s2*. In gel phase peptide causes disorder by its presence. In PC phase most of peptides relatively keep properties of pure lipid. Only I_{24} increases order in membrane. However more fluctuating peptides disorder membrane in the middle

state. The lowest decrease in the amount of dihedral angles in a gel state was induced by I_{24} and V_{24}, while for A_{24} approximately 10 % decrease took place. In LC state peptide causes increase of amount of dihedral angles in trans conformation – maximal increase was caused by presence of I_{24} and L_{24} peptide.

Transitions (Fig. 4) between trans and *gauche* conformations per lipid and per ns occur more often in the liquid-crystalline state than in the gel state. This is typical also for pure lipid membranes. Peptides affect the frequency of these changes and amount of transitions. In gel state all peptides destabilize the surrounding lipids and increase the amount of transitions, but there are differences between various peptides. Fewer transitions are present in the systems containing peptides, which fluctuate more extensively (I_{24}, V_{24}), more transitions are present, if inserted peptide has core composed of Leu. In LC states the peptides decrease the number of transitions. This is similar to the case of order parameters – the peptide influences some configuration of surrounding lipids, which lies between the gel and LC state.

Table 3 shows how the incorporated peptide influences the area per lipid (the area occupied by the peptide is not subtracted). The peptides with small sidechains (A_{24}) have lowest area parameter. The highest area can be found in simulations with L_{24} or I_{24}. Area per lipid is increased with size of aminoacid sidechains and more fluctuating peptide is present (I_{24}). The lowest value exhibits A_{24} peptide and the highest one was typical for I_{24}.

Table 2 Amount of dihedral angles in *trans* conformation

System	% of *trans* dihedral angles; 1st shell	% of *trans* dihedral angles; 2nd shell	System	% of *trans* dihedral angles;1st shell	% of *trans* dihedral angles;2nd shell
pure (DMPC/gel)	87.03±4.75		pure (DPPC/gel)	90.16±4.88	
A_{24}&DMPC/gel	82.45±3.51	86.04±1.82	A_{24}&DPPC/gel	81.68±4.18	88.64±3.50
L_{24}&DMPC/gel	82.53±1.07	84.10±2.34	L_{24}&DPPC/gel	84.64±2.83	90.61±2.20
$(LA)_{12}$&DMPC/gel	80.58±3.53	83.58±3.33	$(LA)_{12}$&DPPC/gel	85.23±1.90	90.73±2.48
I_{24}&DMPC/gel	86.22±2.73	85.72±2.78	I_{24}&DPPC/gel	85.20±1.98	87.15±2.96
P_{24}&DMPC/gel	84.37±4.71	87.48±2.43	P_{24}&DPPC/gel	83.25±2.57	88.57±2.09
V_{24}&DMPC/gel	85.22±2.48	87.17±1.86	V_{24}&DPPC/gel	84.13±2.01	88.58±2.41
pure (DMPC/LC)	75.45±2.71		pure (DPPC/LC)	71.98±2.42	
A_{24}&DMPC/LC	74.23±2.48	75.61±1.43	A_{24}&DPPC/LC	72.30±0.82	72.54±1.27
L_{24}&DMPC/LC	77.06±2.01	77.81±1.89	L_{24}&DPPC/LC	73.05±2.27	72.61±1.05
$(LA)_{12}$&DMPC/LC	75.20±1.36	76.39±2.31	$(LA)_{12}$&DPPC/LC	73.37±1.13	72.08±1.59
I_{24}&DMPC/LC	76.45±2.67	76.01±1.31	I_{24}&DPPC/LC	74.47±2.18	73.76±1.31
P_{24}&DMPC/LC	76.65±1.80	76.53±1.71	P_{24}&DPPC/LC	71.14±1.08	72.65±1.60

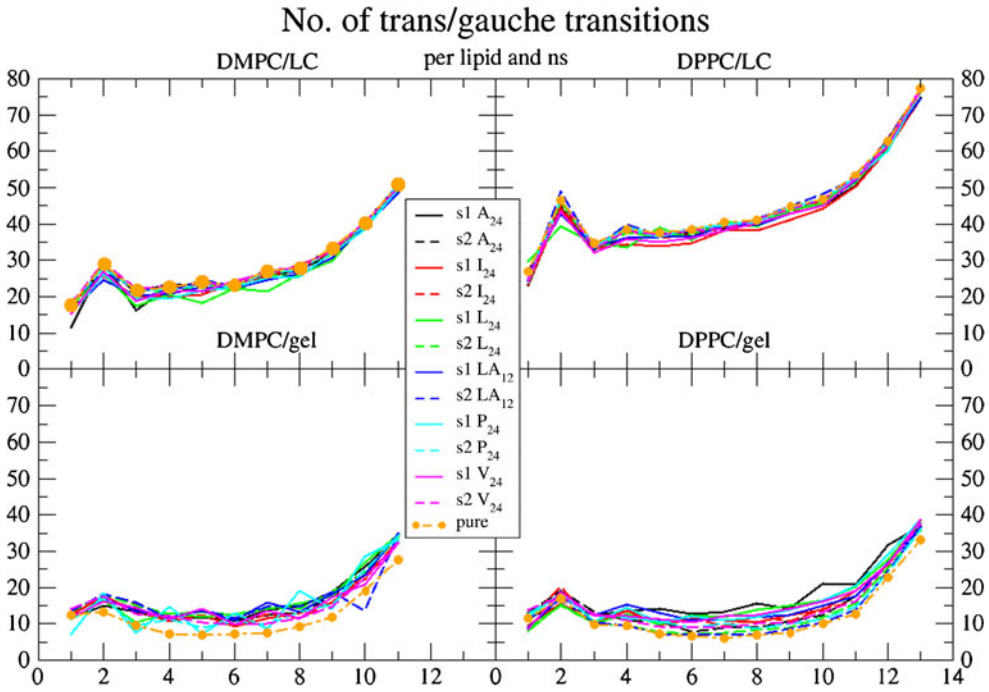

Fig. 4 Number of transitions between *trans* and *gauche* conformations. Frequency of conformation changes depend primarily on temperature, but presence of peptide provides significant modification. In LC state peptide slightly decrease frequency of transitions – mainly I_{24} and V_{24} for DPPC and L_{24} for DMPC. In gel state presence of peptide increases number of transitions, but lowest increase causes I_{24} and V_{24}, while A_{24} or stable L_{24} allows more transitions

The thickness of the membrane (Table 1) is the closest parameter to the effective length of the peptide hydrophobic part from the perspective of the "matching theory". In the Table 1 the effective length (perpendicular to membrane surface) of hydrophobic parts of peptides and the thickness of both lipid shells of the membrane are compared. Lys sidechains can flip in or out and shorten/prolong effective length of peptide (max. to 0.4–0.5 nm). So it is not necessary to keep the same effective length of peptide and 1st shell of lipids to satisfy hydrophobic mismatch.

Table 3 Area per lipid (peptide not subtracted from total area)

System		Area/lipid [nm^2]	System		Area/lipid [nm^2]
DMPC/gel	A_{24}	0.4942	DPPC/gel	A_{24}	0.4718
	I_{24}	0.4956		I_{24}	0.4730
	L_{24}	0.4948		L_{24}	0.4731
	$(LA)_{12}$	0.4953		$(LA)_{12}$	0.4719
	P_{24}	0.4958		P_{24}	0.4739
	V_{24}	0.4945		V_{24}	0.4751
	pure	0.4640		pure	0.4694
DMPC/LC	A_{24}	0.5856	DPPC/LC	A_{24}	0.6207
	I_{24}	0.5881		I_{24}	0.6233
	L_{24}	0.5877		L_{24}	0.6231
	$(LA)_{12}$	0.5872		$(LA)_{12}$	0.6219
	P_{24}	0.5862		P_{24}	0.6206
	V_{24}	0.5873		V_{24}	0.6230
	pure	0.5860		pure	0.6213

The thickness of hydrophobic part of unmodified membranes has a value of 3.6 nm for DPPC/gel, 3.2 nm for DMPC/gel, 3.0 nm for DPPC/LC and 2.6–2.7 nm for DMPC/LC. In all cases the thickness of the second shell (compared with the first shell) are closer to the unmodified membrane: in average it is 3.58 nm for DPPC/gel, 2.93 nm for DPPC/LC, 3.12 nm for DMPC/gel and 2.62 nm for DMPC/LC. In most cases the membrane is 0.3 nm thicker than the effective length of peptide (only for DPPC/LC this difference was around 0.8–1.4 nm; with exception of $(LA)_{12}$ in DPPC/LC – this peptide is in different configuration). Because Lys sidechains are relatively long, it is possible to submerge nearly whole peptide into the membrane and the charged ends of these Lys sidechains can still be in the polar headgroups region. In this case the peptide's tilt is bigger (according to the simulation results) and its effective length is smaller and therefore the membrane became thinner. However, the average membrane thickness does not contain direct information on the orientation of individual lipid chains. Lipid chains can still be longer even in the LC state (higher order parameters, more *trans* positions of dihedral angles), because they can tilt like the peptide.

Tieleman et al. [20] performed 2 ns MD simulation of α-helix with long hydrophobic segments (Flu_{26} and Flu_{34}) in POPC bilayers. They observed considerable extension of the membrane thickness around Flu_{26} peptide and declination by 10°. At the same time, they did not observe extension of the thickness for the peptide Flu_{34} with longer hydrophobic length, but the peptide molecules declined by 25°. As summarized by Killian [24] from experimental and simulation data, there is change of the membrane thickness

near the protein in systems with WALP protein and only a small tilt is created. However Lys flanked peptides such are L_{24}, $(LA)_{12}$ do not change the membrane thickness so extensively and rather increase the peptide's tilt. This agrees with our results, namely the mismatch of thickness of hydrophobic parts is compensated by peptides tilt.

Petrache et al. [10] also discussed possible drawbacks of the molecular dynamics simulations. First there are problems connected with the rather short time of the simulations restricted by several ns. At the same time they received similar results with shorter – around 5 ns and longer – around 10 ns simulations. However, it should be noted that characteristic time of relaxation of phospholipid dipole moments following membrane disturbance by voltage jump lies between the micro- to mili- second scale. Longer time probably corresponds to the collective movement of lipid clusters [25]. Incorporation of the short peptide influences this relaxation time significantly [26]. We can therefore expect that the relaxation time of the short peptides, like L_{24}, should be comparable or even larger than that for phospholipids. Therefore, in order to receive equilibrium state of the peptide in a membrane, the simulations should last an order of microseconds. However, this is beyond the possibilities of current computing technologies.

Despite the large number of limitations MD represents a useful approach for the study of fast conformational movements of peptides and phospholipids in a membrane, though we cannot be sure whether the model system reached equilibrium or not. However, results obtained by MD are consistent with experiments, in respect to inducing hydrophobic mismatch and disordering effect of peptide on the membrane in the gel state.

Conclusions

Our results confirmed the tendency of Lys-flanked peptides to compensate the positive mismatch between peptide and membrane hydrophobic core by tilting. Some of the peptides, however, produce *superhelical* double-twisted structure. This only occurs in the membrane in the gel phase, where only a small hydrophobic mismatch exists. The peptide also alters certain properties of the surrounding lipids such as membrane ordering, the amount of dihedral angles in *trans* conformation and the number of transitions between *trans* and *gauche* conformation. It is likely that these effects should provide some preferable structural state of the peptides in a membrane. The lipid structural state around the peptide is probably between gel and liquid-crystaline state. This effect depends on peptide aminoacid composition. Aminoacids with large sidechains branched at C^{β} (Ile, Val) produces helical structure, which fluctuates more than a poly-Leu helix. This holds also for small sidechains (Ala).

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