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Molecular dynamics simulation of short peptide in DPC micelle using explicit water solvent parameters

Ji-Hun Kim[1,‡], Jong-Jae Yi[2,‡], Hyung-Sik Won[3,‡], and Woo Sung Son[2,*]

[1]College of Pharmacy, Chungbuk National University, Cheongju, Chungbuk 28160, Republic of Korea
[2]College of pharmacy and Institute of Pharmaceutical Sciences, CHA University, 120 Haeyong-ro, Pocheon-si, Gyeonggi-do 11160, Republic of Korea
[3]Department of Biotechnology, College of Biomedical and Health Science, Konkuk University, Chungju, Chungbuk 27478, Republic of Korea

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Abstract Short antimicrobial peptide, A4W, have been studied by molecular dynamics (MD) simulation in an explicit dodecylphosphocholine (DPC) micelle. Peptide was aligned with DPC micelle and transferred new peptide-micelle coordinates within the same solvent box using specific micelle topology parameters. After initial energy minimization and equilibration, the conformation and orientation of the peptide were analyzed from trajectories obtained from the RMD (restrained molecular dynamics) or the subsequent free MD. Also, the information of solvation in the backbone and the side chain of the peptide, hydrogen bonding, and the properties of the dynamics were obtained. The results showed that the backbone residues of peptide are either solvated using water or in other case, they relate to hydrogen bonding. These properties could be a critical factor against the insertion mode of interaction. Most of the peptide-micelle interactions come from the hydrophobic interaction between the side chains of peptide and the structural interior of micelle system. The interaction of peptide-micelle, electrostatic potential and hydrogen bonding, between the terminal residues of peptide and the headgroups in micelle were observed. These interactions could be effect on the structure and flexibility of the peptide terminus.

Keywords Molecular dynamics simulation, nuclear magnetic resonance, peptide, micelle, hydrogen bonding, dodecylphosphocholine

Introduction

Molecular dynamics simulations have proven to be a useful tool for elucidating the relationship between the structures and dynamics of peptides and proteins.[1-3] And various kinds of models of membrane mimetic systems have been employed to simulate membrane peptides and proteins in explicit solvents.[4-6] The properties of dynamics in solvents and membrane mimetic systems are crucial to structures and functions of membrane peptides and proteins.[7-9]

Short antimicrobial undecapeptide analogue, A4W, from Asian frog, Rana rugosa was used for molecular dynamics simulations in an explicit dodecylphosphocholine (DPC) micelle. The solutions structure of A4W peptide was solved using nuclear magnetic resonance spectroscopy (NMR) in sodiumdodecylsulfate (SDS) micelle, previously.[10]

‡ These authors contributed equally.
* Address correspondence to: **Woo Sung Son,** College of Pharmacy and Institute of Pharmaceutical Sciences, CHA University, 120 Haeryong-ro, Pocheon-si, Gyeonggi-do 11160, Republic of Korea, Tel: 82-31-850-9398; Fax: 82-31-850-9398; E-mail: wson@cha.ac.kr

The elucidated structure presented the key model of interdependence between a membrane mimetic environment and physicochemical properties of A4W peptide. But it is necessary to obtain additional information of the detailed mechanism and interactions between membrane mimetic environment and peptide. Especially, the effect of water molecules on micelle-peptide system could be key to understand the action mechanism of antimicrobial peptide in real bio-membrane in molecular level.

Table 1. Molecular systems used for molecular dynamics simulations.

Molecular systems/conditions	*Properties*	*Model*
peptide	12 residues	NMR structure
water	Explicit solvent	TIP3P
Membrane mimetic molecules	DPC	
Temperature (K) at equilibrium	300	-
Time for simulation (ps)	20	-
Constant pressure (atm)	1	-

Experimental Methods

NMR and structure determination- NMR experiments for structural restraints and computational calculation were performed with the protocols as reported previously.[10-12]

Molecular dynamics simulation- All molecular dynamics simulations were carried out using the AMBER9 program[13] and the GROMACS[14-17] for peptide and micelles and using the TIP3P water model. The A4W peptides were placed in a periodically repeating box containing a pre-equilibrated membrane mimetic system composed of DPC lipids and water molecules. Several simulations were performed with different numbers of peptides, lipids, and water

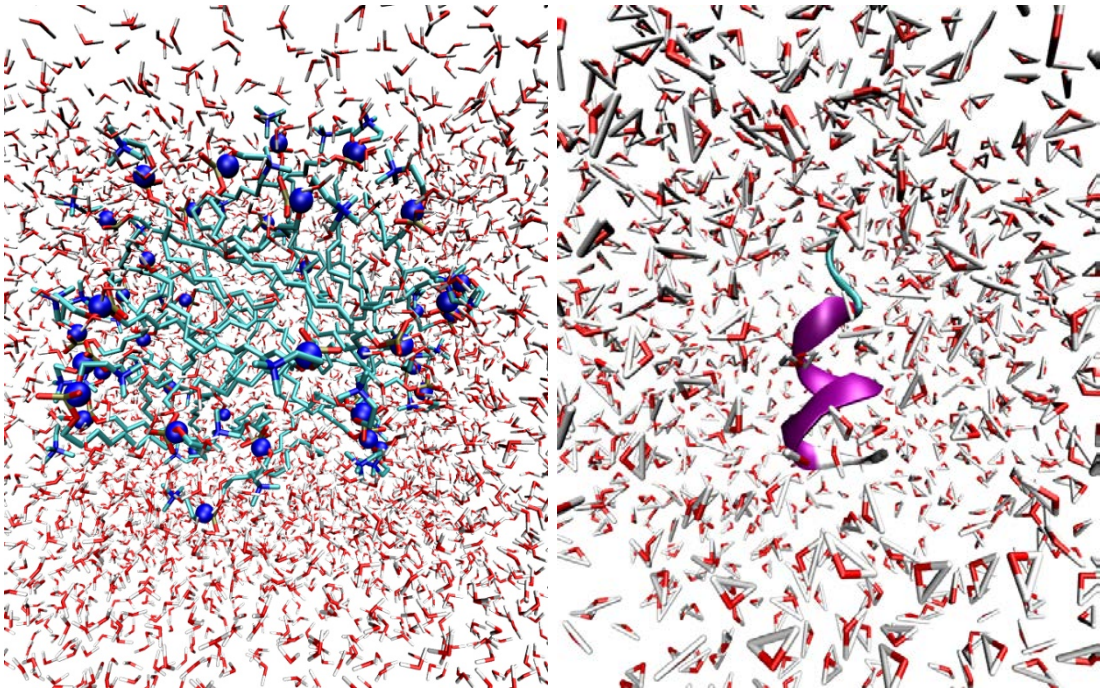

Figure 1. Energy minimized models of DPC micelles (left) and A4W peptide (right). The whole systems were minimized in TIP3P explicit water molecules using AMBER9. The water molecules were represented as triangle with red (oxygen) and white (hydrogen) color, respectively. Hydrophilic headgroups and hydrophobic tails were shown by blue ball and green stick, respectively.

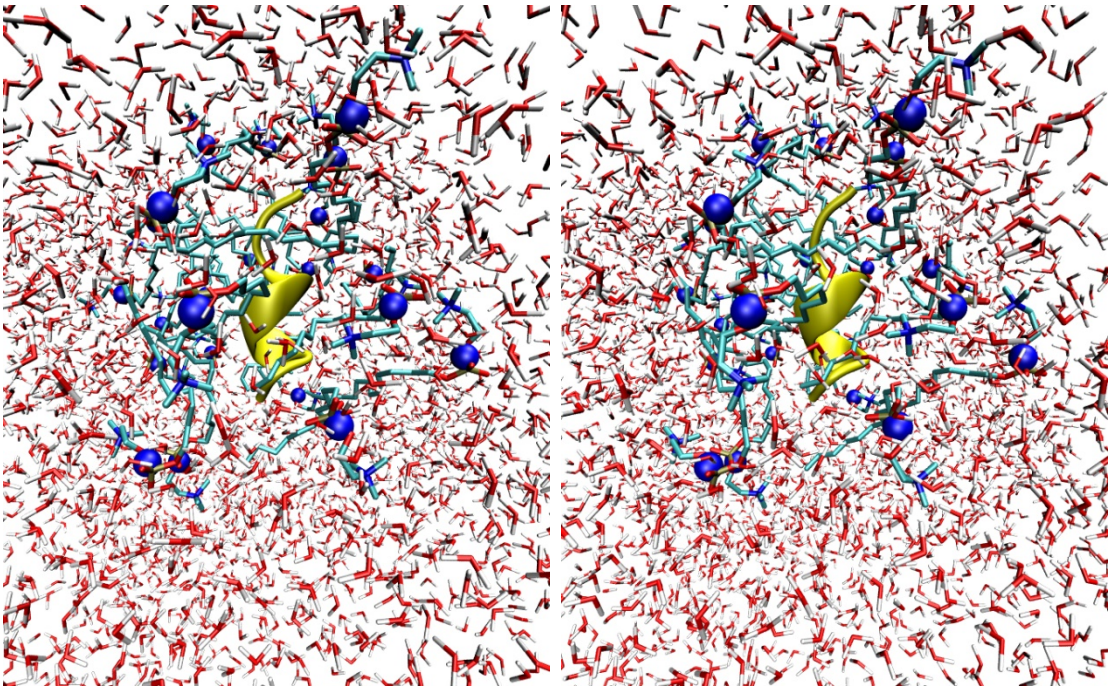

Figure 2. Snapshots at different times along the simulation of a system composed of DPC lipids, water molecules, and A4W peptide. Colors and representations are the same as Figure 1. The position of the peptide and lipids at initial stage (0 ps, left) and one of the positions of the peptide after a 20 ps simulation (right) were shown, respectively.

molecules. The peptides were near center of the micelle, such that the A4W peptides bound mostly to core of the micelle. And then configurations were away from equilibrium. The overall temperature of the water, lipids, and peptides was kept constant, coupling independently each group of molecules at 300 K with a Berendsen thermostat. The pressure was coupled to a Berendsen barostat at 1 atm separately in every dimension. The temperature and pressure time constants of the coupling were 0.2 and 0.4 ps, respectively. The integration of the equations of motion was performed by using a leap frog algorithm with a time step of 2 fs (Table 1.).

Results and Discussion

Here, we present the initial process of single A4W peptide (FLGWLFKVASK) penetration into DPC membrane mimetic using MD simulation (Figs 1 and 2). The type of secondary structure in α−helix (WLFKVA). DPC is a most commonly used detergent to implement the membrane environment for structural studies.[18] The template structure of A4W coordinated to SDS micelle was previously determined using NMR. However, SDS is biologically harsh to be used instead of biophysical membrane environment, and sometimes physical characteristics of peptide were changed according to the kind of membrane mimetic.[19] For these reasons, MD simulation of A4W coordinated to more mild detergent, DPC, was essential to elucidate the initial motion of peptide when it inserted into membrane.

The RMS difference plot showed that the backbone residues of peptide are either solvated using water and DPC lipids (Fig. 3). From the monitoring of energy and particle density changes, the A4W-solvent-micelle system seems to be stabilized within 20 ps after starting simulation (Fig. 4). Compared with the residues of N-terminus, residues of C-terminus were more stable at equilibrium state. These properties could be a critical factor against the insertion mode of interaction and suggest the possibility of the connection with hydrogen bonding. Most of the peptide-micelle interactions come from the hydrophobic interaction between the side chains of peptide and the structural interior of micelle system. In order to obtain the precise parameters of molecular dynamics simulations of peptide-micelle-water system, it is essential to consider the multitude of simulation protocols and traits.

Several membrane disrupting mechanisms including carpet, barrel-stave, and toroidal pore model have been suggested, however, exact mechanism has not been elucidated yet.[20] Although the resultant MD simulation elucidated single peptide motion in membrane environment in the present work was not enough to pin down the membrane disrupting mechanism of A4W, some result which can be a clue to sketch the disrupting model were presented. The things that the single peptide is capable to insert into the membrane environment and N-terminus has more mobility than C-terminus indicate that toroidal pore is likely to be a penetrating model of A4W peptide.

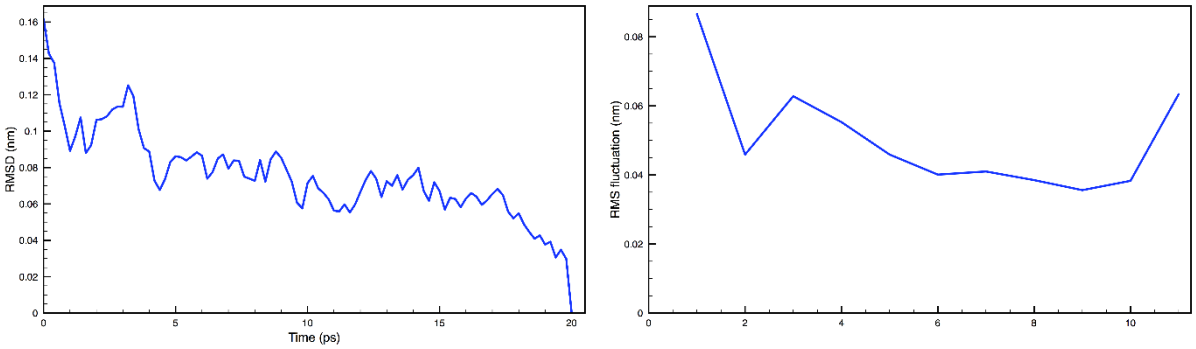

Figure 3. RMS difference for A4W-solvent-micelle system during molecular dynamics simulation. The least square fit of position of C-alpha was calculated in model after MD (left), and RMS fluctuation of A4W in solvent-micelle system was calculated in fs scale (right).

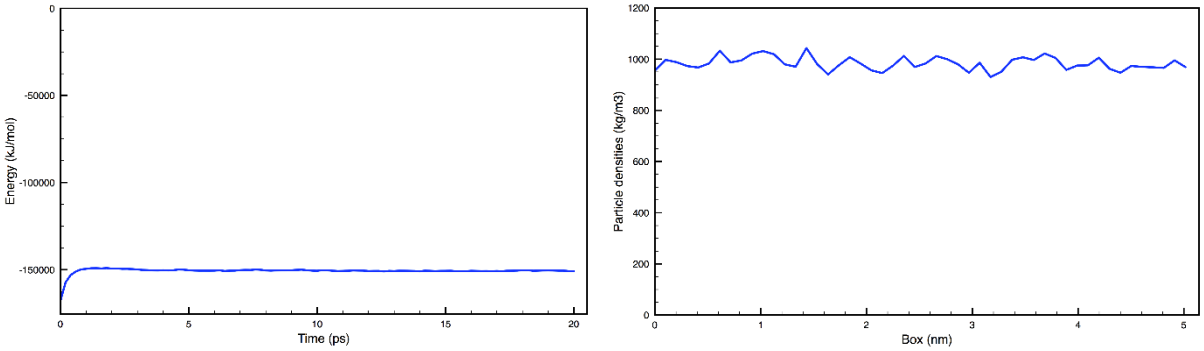

Figure 4. Total GROMACS energies (left) and partial densities (right) of A4W-solvent-micelle system were represented in ps time scale and in nm periodic box scale.

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