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Regulation of channel function due to physical energetic coupling with a lipid bilayer

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ABSTRACT

Regulation of membrane protein functions due to hydrophobic coupling with a lipid bilayer has been investigated. An energy formula describing interactions between lipid bilayer and integral ion channels with different structures, which is based on the screened Coulomb interaction approximation, has been developed. Here the interaction energy is represented as being due to charge-based interactions between channel and lipid bilayer. The hydrophobic bilayer thickness channel length mismatch is found to induce channel destabilization exponentially while negative lipid curvature linearly. Experimental parameters related to channel dynamics are consistent with theoretical predictions. To measure comparable energy parameters directly in the system and to elucidate the mechanism at an atomistic level we performed molecular dynamics (MD) simulations of the ion channel forming peptide–lipid complexes. MD simulations indicate that peptides and lipids experience electrostatic and van der Waals interactions for short period of time when found within each other's proximity. The energies from these two interactions are found to be similar to the energies derived theoretically using the screened Coulomb and the van der Waals interactions between peptides (in ion channel) and lipids (in lipid bilayer) due to mainly their charge properties. The results of *in silico* MD studies taken together with experimental observable parameters and theoretical energetic predictions suggest that the peptides induce ion channels inside lipid membranes due to peptide–lipid physical interactions. This study provides a new insight helping better understand of the underlying mechanisms of membrane protein functions in cell membrane leading to important biological implications.

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1. Introduction

Membrane protein conformational changes can be reflected through opening/closing transitions in lipid bilayer hosted ion channels [1]. In many such cases a bilayer perturbation occurs near proteins [2] (see Supp Fig. 1). The bilayer possessing elastic properties [3] incurs an energetic cost ΔG^0_{def} which contributes to the overall free energy difference $\Delta G^{I\rightarrow II}_{tot} = \Delta G^{I\rightarrow II}_{prot} + \Delta\Delta G^{I\rightarrow II}_{def}$ between two protein states e.g., I and II. The free energy contribution $\Delta G^{I\rightarrow II}_{prot}$ is the energetic cost of the protein conformational change *per se* and $\Delta\Delta G^{I\rightarrow II}_{def}$ is the bilayer deformation energy difference between two states. In this bilayer-protein interaction, bilayer deformation appears to be a regulator of integral membrane protein functions. To understand this phenomenon, we experimentally and theoretically investigate how lipid membranes with different mechanical, geometrical and electrical properties regulate the integral ion channel energetics using two structurally different channels, namely β-helical gramicidin A (gA) [4] and 'barrel-stave' pore type alamethicin (Alm) [5,6] (Supp Fig. 1).

Molecular mechanisms of peptide effects on membranes have been investigated especially by performing molecular dynamics (MD) simulations of both peptides gA- and Alm-lipid complexes. Here we report computational results for any possible peptide–lipid physical interactions, which might play crucial roles behind the creation of stable ion channels that are hydrophobically coupled to host bilayers. We specifically focus on the peptide–lipid binding energies and parameters related to stability of the complex. These MD results also shed new light on the complex interactions between stable structure (e.g., biomolecules) and liquid crystal structure (e.g., membrane), a very important and still unresolved problem in biophysics and soft condensed matter physics.

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The MD simulation was initiated based on a strong background of theoretical and experimental understanding of the phenomenological aspects of the problem. In gA channel formation the association of two trans-bilayer gA monomers is governed by the dimerization coefficient: $K_D = [D]/[M_g]^2 = k_1/k_{-1} = \exp\{-(\Delta G^0_{prot} + \Delta G^0_{def})/k_B T\}$, where $[M_g]$ and $[D]$ are monomer and dimer concentrations; and k_1 and k_{-1} are rate constants determining the gA channel appearance rate ($f_g = k_1 \cdot [M_g]^2$) and lifetime ($\tau = 1/k_{-1}$) [7]. k_B and T are the Boltzmann constant and absolute temperature, respectively. Since the bilayer deformation energy ΔG^0_{def} is sensitive to the hydrophobic mismatch ($d_0 - l$) between bilayer thickness (d_0) and gA channel length (l), the bilayer responds to its deformation by imposing a restoring/channel-dissociation force F_{dis} on the edges of a channel [7–9]. Increasing F_{dis} is reflected in a decreasing τ and vice versa, channels thus become molecular force transducers [7]. Within limits, the channel structure can be considered invariant when d_0 is varied [10], meaning gA channel is more rigid than a lipid bilayer. All-atom MD simulations of gA in bilayers [11] show how lipid head groups organize themselves in the region of hydrophobic free length $d_0 - l$. Potential-of-mean-force calculations [12] suggest that trans-membrane protein interactions are regulated by a hydrophobic mismatch equivalent to $d_0 - l$. The calculation of F_{dis} has been a long-standing challenge. Based on a well-established theory of elastic bilayer (EB) deformation [13] ΔG^0_{def} has been found to be approximately changing as a quadratic function of $d_0 - l$ [13,14] but subsequent developments [15–18] resulted in introduction of lipid intrinsic curvature c_0 (whose positive and negative changes correspond to increases and decreases of the hexagonal lipid phase, respectively, and any such local curvature profile generally controls the lipid packing energy profiles in bilayers) [19] into the expression for ΔG^0_{def} which is now considered to be a quadratic function of $d_0 - l$ and intrinsic curvature c_0, $\Delta^0_{def} = H_B \cdot (d_0 - l)^2 + H_X \cdot (d_0 - l) \cdot c_0 + H_c \cdot c_0^2$. Consequently, F_{dis} changes linearly with $d_0 - l$ and c_0 [7,8]: $F_{dis} = -(-(\partial/\partial(d_0 - l))\Delta G^0_{def}) = 2H_B \cdot (d_0 - l) + H_X \cdot c_0$. Here H_B, H_X and H_c are phenomenological elastic constants. Using 'elastic parameters' in a fluid-like membrane is a good first-order approximation that works well within the limitations of a linear theory. To extend the applicability of the theory to a nonlinear regime, we use the 'screened Coulomb interaction' (SCI) [9,20]. The interaction energy between a gA channel and a host bilayer has been calculated based on experimentally observable parameters such as d_0 [21], lipid head group dimension [22], l [21], lipid charge q_L [23] and dielectric parameters of the lipid bilayer core [24]. Considering $l < d_0$, the channel extends its Coulomb interaction towards lipids placed at the bilayer's nearest resting thickness (Supp Fig. 1). A gA channel directly interacts with a nearest-neighbor lipid by Coulomb forces and this lipid interacts directly with the next-nearest-neighbor lipid but this second lipid's interaction with the channel is screened by the channel's nearest-neighbor lipid. The interaction between the third-nearest neighbors and the channel is screened by the lipids in between. The general form of SCI is:

$$V_{sc}(\vec{r}) = \int d^3k Exp\{i\vec{k} \cdot \vec{r}\} V_{sc}(\vec{k}) \quad (1)$$

whose Fourier transform is [25]:

$$V_{sc}\left(\vec{k}\right) = \frac{V(\vec{k})}{1 + \frac{V(\vec{k})}{2\pi k_B T} n} \quad (2)$$

where $V(k) = (1/\varepsilon_0 \cdot \varepsilon_r) q_g q_L / k^2$ is the direct Coulomb interaction between a gA monomer (with a charge q_g) in a channel and the nearest-neighbor lipid. $k \approx 2\pi/r_{LL}$, r_{LL} is the average lipid–lipid distance [22], assumed also be the distance between the channel's longitudinal edge and the nearest lipid head group. n Is lipid density ~1/60 Å^2. Obviously, $k_B T \approx 1.38 \times 10^{-23}$ J/K (300 K). Here, ε_0 is the dielectric constant in vacuum and ε_r (~2) is the relative dielectric constant inside the membrane [24] where all peptide–lipid interactions are assumed to take place.

Theoretical calculation of a channel's energies and their direct correlation with experimentally observable channel stability. The binding energy between two monomers in a gA channel ($U_{g,g}$) is due to the Lennard–Jones and Coulomb potentials [26]. gA channel stability τ does not primarily follow the modest change in $U_{g,g}$ due to change of gA monomer's charge profile which has been found valid in case of binding of amphiphiles, anti-fusion and AMPs with channels in a varied membrane environment (manuscript in preparation). Monomer–monomer binding in a gA channel is therefore comparatively very rigid. These observations together with those presented in [10] suggest that a change in τ is mainly due to the change in the gA channel bilayer coupling energy ($U_{g,bilayer}$) even though the total binding energy is $U(r) = U_{g,g} + U_{g,bilayer}$. Here, $U_{g,bilayer}$ is proportional to the 1st, 2nd, etc. order term in the expansion of $V_{sc}(r)$ for the hydrophobic mismatch to be filled by single, double etc. lipids representing 1st, 2nd, etc. order screening, respectively (details in [9,20]). ΔG^0_{prot} and ΔG^0_{def} are proportional to $U_{g,g}$ and $U_{g,bilayer}$, respectively. These energies can be detected using MD simulation. F_{dis} therefore originates from mechano-electrical properties of membranes [9,20].

2. Materials and methods

Detailed materials and methods for numerical computation and experimental techniques are [9,20]. To address SCI's various lipid order screening $d_0 - l$ was experimentally [9] varied by changing d_0 using lipids with varying acyl chain length or gA monomers of different lengths or both, which changes F_{dis} and as a result τ (see Supp Fig. 2). Addition of phosphoethanolamine fractionally with phosphocholine introduces negative curvature [19] in bilayer with comparable d_0 [27]. Further parametric information in peptide-membrane interactions can be obtained in various places e.g., [28–32].

For MD simulations to investigate AMP–lipid interactions in molecular level we modeled dynamical changes of *in silico* peptide–lipid interactions following the protocol used *in silico* modeling of CD–lipid interactions [33]. Based on Monte Carlo concept, we considered five different relative locations and orientations randomly generated in each AMP–lipid complex as initial structures for MD simulations to increase sampling size for better statistical analysis. For each location- and orientation-specific complex, a 10 ns explicit water MD simulation at temperature 300 K in an aqueous solution at pH 7 was performed. We applied the software package Amber 11 (Amber force field ff03) [34]. The explicit water TIP3P model was used to simulate solvent effects. The force field parameters for AMPs and lipids (PC and PS) were generated using an Amber module antechamber [35,36]. The parameters for AMPs were compared with those generated for colchicine [37] and taxol [38] respectively. Both studies [37,38] have shown these parameterizations lead to simulations that are consistent with experiments. Therefore, similar results based on these parameterizations are expected. In simulation, first, twenty complexes were energy minimized using the steepest descent method for the first ten cycles and then followed by a conjugate gradient for another 1000 cycles. We then applied Langevin dynamics during the process of heating up the system for 200 ps with the energy minimized complex, in which AMP and lipid molecules were being restrained using a harmonic potential with a force constant $k = 100$ N/m. Afterward, we introduced pressure regulation to equilibrate water molecules around the complex and to reach an

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