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Charged Protein-Lipid Interactions: Membrane Thickness

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Abstract

The actions of integral and peripheral membrane proteins, as well as cell disrupting peptides, are known to be influenced by charged amino acids. Although atomistic molecular dynamics studies have shed light on the mechanics of charged protein group membrane binding and translocation, the impact of the complete range of membrane Physio-chemical characteristics and topologies has yet to be investigated. We investigated the movement of an Arginine (Arg) side chain analogue across saturated phosphatidylcholine (PC) bilayers with hydrocarbon tail lengths ranging from 10 to 18 carbons in this paper. With increased penetration into the hydrocarbon core, the free energy profiles all show steep climbs, with predictable shifts between bilayers of varying thickness, resulting in a barrier reduction from 26 kcal/mol for 18 carbons to 6 kcal/mol for 10 carbons. We see narrow transmembrane pores and associated plateaus in the free energy profiles for lipids with 10 and 12 carbons.

***Keywords:** Proteins; Peptides; Atomistic; Membrane; Phosphatidylcholine; Lipids*

Introduction

Biological membranes contain a variety of proteins that perform important roles as well as protective shells that efficiently impede uncatalyzed permeation of polar and charged substances. This viewpoint has held sway for decades, and it is based on the energetics of ion translocation through an oily membrane slab. Recent research suggests that cell membranes may not be as impenetrable as previously thought. Because charged protein groups like Arginine (Arg) and Lysine (Lys) can play critical roles in protein structure and function, as well as the actions of a variety of cell-perturbing peptides, it's critical to understand how charged protein groups interact with biological membranes at the molecular level. Biological membranes are frequently shown as bilayers of lipid molecules forming non-polar sheet-like regions. Charged molecules (of several tens of kcal/mol) must dehydrate when they pass the membrane interface due to the rigid slab model's enormous barriers. The so-called "paddle model" of voltage-gated ion channel activation, which predicted lipid-exposed migration of multiple charged Arg residues across the lipid membrane, has lately challenged this idea. It was also called into doubt when cell biology tests using membrane protein synthesis's translocon machinery revealed low energy costs for including Arg during a transmembrane protein segment. Incorporating Arg on a host-barrel protein (OmpLA) at the middle of a 12-carbon Dilauroyl-PC (DLPC) membrane has recently been suggested at a cost of just 4 kcal/mol. This apparent discrepancy between theory and experiment has spurred a heated debate over how to interpret these findings, leading to a series of research that has revealed fresh insight into the electromechanical behavior of lipid membranes. The simplistic continuum definition of membranes remained constant for nearly half a century in the absence of molecular-level descriptions of membrane charge transport systems. All-atom molecular dynamics (MD) studies, on the other hand, have revealed some entirely unexpected (though foreseen by A. Parsegian over 40 years ago) Physico-chemical behaviour connected with lipid bilayer deformability. Water and lipid head groups are now being drawn towards the non-polar membrane core by the presence of charged molecules. Because the molecule never totally dehydrates but must pay a price of deforming the membrane, the resulting free energy profile (or potential of mean force, PMF) for charge translocation is considerably different from earlier continuum models. This unexpected result has many serious implications, including a lack of sensitivity of translocation energetics to the chemical identity of the charged molecule or protein group (Vorobyov et al., in preparation), the binding of a counter-ion of anionic lipid head group, and even the membrane's dipole potential. These findings have important implications for biological processes involving charge–membrane interactions, and they have paved the way for a deeper understanding of membrane transport processes. Studies of membrane charge transfer using all-atom MD have traditionally been limited to well-characterized

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single-component model lipid bilayers (e.g. 16 carbon, dipalmitoyl-PC, DPPC). Biological membranes, on the other hand, can contain a vast range of lipid types, with compositions that differ significantly from membrane to membrane and even within domains within the same membrane. The shape and mechano-elastic properties of the membrane are influenced by lipid content, which might affect protein partitioning and activity. We had predicted that electrostatic interactions would play a significant role in charge–membrane interactions, e.g. via neutralisation by binding to a charged lipid, out of all the possible changes in membrane characteristics. However, due to membrane deformations that result in very comparable interactions with zwitterionic and anionic lipids, we recently revealed that anionic lipids have a very modest effect on the mobility of Arg side chains in membranes. While there are still more lipid chemistries to investigate, membrane structure, particularly thickness, is the next likely suspect for influencing charge–membrane interactions.

Conclusion

We used atomistic simulations to study the translocation of MguanH+, an Arg side chain analogue, over lipid membranes with varying hydrophobic thickness. MguanH+ causes identical membrane deformations in all bilayers by drawing water molecules and lipid head groups into their hydrocarbon cores, according to our findings. Except for a shift caused by the difference in bilayer hydrophobic thickness, the solvation, H-bonding, and interaction energies of MguanH+ in both membranes are relatively comparable. The deformations and ion microenvironments in all bilayers are substantially comparable when the data are displayed as a function of distance from the interface rather than the bilayer centre.