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Electromechanical Properties of Lipid Bilayers in Peptide-Lipid Interactions: Clinical Applications

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Abstract

Despite the amazing diversity and complexity of living systems, all life shares the presence of a semi-permeable lipid membrane. Throughout evolution, this permeability has been finely regulated by the function of proteins that form ion channels. Similarly, some peptides can stabilize by forming aqueous pores in a dose-dependent manner. At high concentrations, however, these peptides can compromise the integrity of the membrane, destroying it. Given this behavior, a huge diversity of antimicrobial peptides and lipo-peptides has been identified. Understanding the physical-chemical principles of their interactions with lipids can contribute to the design of synthetic peptides with antimicrobial activity as an alternative to the use of conventional antibiotics.

Keywords: Lipid Bilayers; Lipo-peptides; Synthetic Peptides; Antimicrobial Activity

Abbreviations: MS: Mechano-Sensitive; TM1: N-Terminal Domain; PFPS: Pore-Forming Peptides; AMPS: Antimicrobial Peptides; P/L: Peptide-To-Lipid Ratio; LPS: Lipo-Peptides.

Introduction

Every cell responds to the mechanical stimuli from its environment to a greater or lesser degree. This class of responses can be considered, therefore, as one of the most ancient, probably universal in all living organisms. Mechano-sensitive (MS) ion channels have developed the specific ability to respond, in a regulated manner, to this class of stimuli [1]. However, several other proteins also respond to this class of stimuli to a greater or lesser degree [2]. Thus, to better understand the function of any protein inserted in any lipid membrane, studying the physicochemical context surrounding them is always important. The physical properties that, as a material, the lipids in which they are immersed have, determine directly but subtly the modulation of the activities that membrane proteins exhibit [3]. It is now known that the lipid component of biological membranes determines, for example, the distribution, organization, and functioning of distinct and diverse membrane proteins, importantly MS ion channels. In general terms, the regulation of this type of membrane protein is the result of specific lipid-protein interactions, general bilayer-protein interactions, and, on the other hand, interactions at the hydrophobic-aqueous medium interface. Such interactions occur mainly due to the coupling between the hydrophobic phase of the bilayer with respect to the hydrophobic domains of these membrane proteins and, therefore, are a function of the material properties of the bilayer as a whole: its thickness, degree of compaction, intrinsic curvature, viscoelasticity, stiffness, asymmetry, surface charge and ultimately, chemical composition [4-6].

In this context, to study the material properties that lipid bilayers exhibit and their response to different physical

variables such as temperature, pressure, pH, or the ionic strength of the aqueous medium in which they are formed, it is necessary to understand the interactions between the building blocks, that is, the lipids and their aqueous medium. In responding to these physico-chemical factors, many membrane proteins, notably ion channels, directly respond to the thermo-tropic and mechanical state of lipids [7,8], particularly channels considered intrinsically mechano-sensitive [9]. Likewise, it is known that the dynamic nature of lipids enables them to form aqueous pores [10]. The formation and stability of these pores largely depend on the lipid thermo-tropic behavior [11].

MS channels in prokaryotes function mainly in cellular osmoregulation by forming large aqueous pores under events of hypo-osmotic shocks [12] and it is interesting that, compared to these, many eukaryotic MS channels fulfill similar functions, although their function is only inferred from many homologs [13,14]. Taking as an archetypal model the structure of the bacterial channel MscL of Escherichia coli, Ghazi et al. [15] studied separately the two domains of the EcMscL protein and proved that the N-terminal domain (TM1) can form aqueous pores in liposomes, which respond in an unregulated manner to lateral membrane tension. Additionally, Clayton, et al. [16] have achieved the *In vitro* chemical synthesis of the EcMscL channel and the ortholog from Mycobacterium tuberculosis. Notably, in both cases, these proteins are fully functional. This suggests that synthetic peptides can mimic the activity of biological MS channels.

Lytic Peptides

Nature always surprises us. A wide variety of pore-forming peptides (PFPs) such as alamethicin, melittin, magainin, and lipo-peptides such as dapto-mycin or feng-mycin can insert themselves into membranes, aggregating into aqueous pore-forming complexes. It is worth mentioning that the study of these peptides and other similar ones is also an interesting antimicrobial alternative [17-19]. Remarkably, using giant liposomes, it has been proven that the presence of antimicrobial peptides (AMPs) such as melittin from Apis mellifera venom (GIGAVLKVLTTGLPALISWIKRKRQQ) (Figure 1), induces the formation of aqueous pores and even induce vesicular lysis, depending on the peptide-to-lipid ratio (P/L) [20]. Therefore, at appropriate concentrations, melittin can form stable pores. Under such conditions, these model systems are able of dissipating osmotic gradients, responding to increases in membrane tension, a mechanism analogous to that exhibited by bacterial MS channels [1,2,9]. Interestingly, the activity of this class of natural peptides can also be directly compared to that shown by some synthetic amphipathic peptides, such as peptides of the α-18L class (GIKKFLGSIWKFIKAFVG) (Figure) that exhibit similar osmo-protective behavior [21]. Once inserted into the membrane, these peptides perturb the bilayer and create peptide nucleation sites from which aqueous pores are formed responding to micro-environmental osmotic changes and releasing several osmolytes. Therefore, at least potentially, it is possible to synthesize peptides that can directly simulate the activity of forming aqueous pores with a possible osmo-regulatory function or induce lysis at high concentrations.

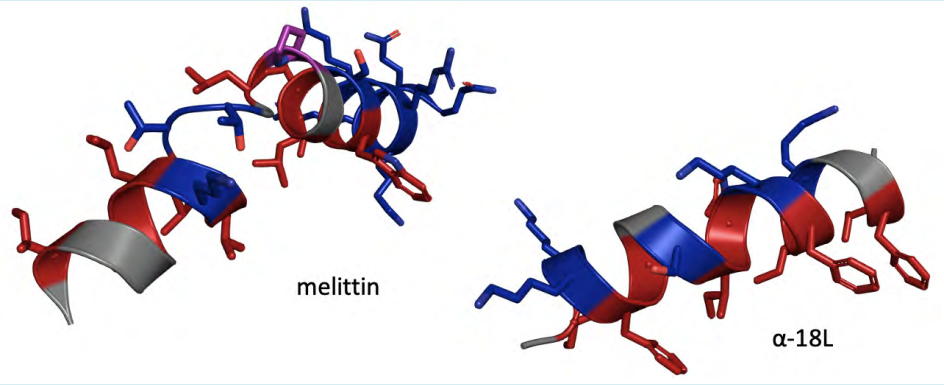

Figure 1: Melitin from Apis mellifera venom (GIGAVLKVLTTGLPALISWIKRKRQQ) & peptides of the α-18L class (GIKKFLGSIWKFIKAFVG).

À la carte Peptides

The perspective to design peptides with antimicrobial activity is not new [22,23]. However, albeit research efforts have focused mainly on characterizing peptides obtained directly from their biological sources or synthetic ones, only a few of them have been approved by the FDA [24]. It becomes evident that it is necessary to continue characterizing these potential antimicrobial agents at the biophysical level to propose using AMPs and similar compounds such as lipo-peptides (LPs) and as alternative antibiotics. Indeed, Cubicin® (daptomycin), an LP that induces membrane

permeability in Gram(+) bacteria, including methicillin-resistant Staphylococcus aurous and vanco-mycin resistant Enterococci bacteria is the first LP approved as an intravenous drug by the FDA for the treatment of serious skin (approved in 2003) and bloodstream infections (approved in 2006) [25]. Cubist Pharmaceuticals has devoted a great deal of effort to obtaining compounds derived from dapto-mycin by chemical or biosynthetic methods. The cyclic lipo-peptide CB-183,315 has been characterized *In vitro* and *In vivo* against Clostridium difficile, showing good quality standards and activity in hamsters; it is now in phase 3 clinical trials for the treatment of C. Difficile-associated diarrhea and it is pending to be finally approved by the FDA [26,27].

Conclusion

The emergence of pathogens resistant to conventional antibiotics is increasing rapidly and globally. This problem has raised the alternative of using other antimicrobial control strategies. Antimicrobial peptides and lipopeptides are promising alternatives that target biological membranes by diverse mechanisms of action, including membrane permeabilization and detergent effect. Studying the factors that determine these interactions at the molecular level will allow obtaining the necessary knowledge for the intelligent design of synthetic peptides with potential activity against several multidrug-resistant strains. Maintaining research efforts in the study of peptide-lipid interactions will surely contribute to the development of a new generation of antimicrobial therapies and increasingly effective control strategies in the face of the growing problem of bacterial multidrug resistance.

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