Solid State Nuclear Magnetic Resonance ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Solid State Nuclear Magnetic Resonance

journal homepage: www.elsevier.com/locate/ssnmr

Trends

Membranes, peptides, and disease: Unraveling the mechanisms of viral proteins with solid state nuclear magnetic resonance spectroscopy

Matthew T. Eddy [a], Tsyr-Yan Yu [b,*]

[a] Department of Integrative Structural and Computational Biology, The Scripps Research Institute, La Jolla, CA 92037 USA
[b] Institute of Atomic and Molecular Sciences, Academia Sinica, No. 1 Sec. 4. Rooseverlt Rd., Taipei, 10617, Taiwan

ARTICLE INFO

Article history:
Received 5 February 2014
Received in revised form
22 April 2014

Keywords:
Membrane associated viral peptides
Membrane associate viral protein
ssNMR
Protein structure and function

ABSTRACT

The interplay between peptides and lipid bilayers drives crucial biological processes. For example, a critical step in the replication cycle of enveloped viruses is the fusion of the viral membrane and host cell endosomal membrane, and these fusion events are controlled by viral fusion peptides. Thus such membrane-interacting peptides are of considerable interest as potential pharmacological targets. Deeper insight is needed into the mechanisms by which fusion peptides and other viral peptides modulate their surrounding membrane environment, and also how the particular membrane environment modulates the structure and activity of these peptides. An important step toward understanding these processes is to characterize the structure of viral peptides in environments that are as biologically relevant as possible. Solid state nuclear magnetic resonance (ssNMR) is uniquely well suited to provide atomic level information on the structure and dynamics of both membrane-associated peptides as well as the lipid bilayer itself; further ssNMR can delineate the contribution of specific membrane components, such as cholesterol, or changing cellular conditions, such as a decrease in pH on membrane-associating peptides. This paper highlights recent advances in the study of three types of membrane associated viral peptides by ssNMR to illustrate the more general power of ssNMR in addressing important biological questions involving membrane proteins.

Contents

Abbreviations: CD4, Cluster determinant 4; CCP, Cell-penetrating peptide; CCR5, Human chemokine receptor 5; CXCR4, C-X-C chemokine receptor type 4; FP, Fusion peptide; HN, Hemagglutinin neuraminidase; HETCOR, Heteronuclear correlation experiment; DMPC, 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine; DMPG, 1,2-ditetradecanoyl-*sn*-glycero-3-phospho-(1′-*rac*-glycerol) (sodium salt); DTPC, 1,2-di-*O*-tetradecyl*sn*-glycero-3-phosphocholine; DTPG, 1,2-di-*O*-tetradecyl*sn*-glycero-3-phospho-*rac*-(1-glycerol) sodium salt; DNP, Dynamic nuclear polarization; DPC, Dodecyl-phosphocholine; HA, Influenza haemagglutinin; HIV, Human immunodeficiency virus; LPPG, 1-palmitoyl-2-hydroxy-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)]; PIV, Paramyxovirus parainfluenza virus; POPC, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine; POPG, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)]; REDOR, Rotation-echo double resonance experiment; SDS, Sodium dodecyl sulfate; TAT, The trans-activator of transcription; VFP, Viral fusion peptide

* Corresponding author. Fax: +886 2 23660200.
E-mail address: dharmanmr@gate.sinica.edu.tw (T.-Y. Yu).

http://dx.doi.org/10.1016/j.ssnmr.2014.04.002
0926-2040/

1. Introduction

Membrane-associated peptides and proteins not only fulfill critical biological functions within membrane environments but can also directly manipulate their membrane environments to drive biological events. A huge variety of cellular processes depend on the interaction of peptides and proteins with their surrounding membrane environment, including vesicle formation, exocytosis, endocytosis and the transport of hydrophilic molecules such as DNA or RNA across the hydrophobic cell membrane. Peptide–membrane interactions can also be hijacked by viruses. Enveloped virus particles express membrane proteins that fuse viral and host cell membranes during viral replication [1]. Further, some peptides that selectively target bacterial membranes have been found to have promising antimicrobial properties [2–13]. Thus membrane-associated peptides and proteins are of considerable interest as both potential therapeutics and therapeutic targets. A spectacular amount of ssNMR research is ongoing into a huge variety of membrane-associated and membrane-embedded peptides and proteins; this review focuses on peptides expressed by viruses that target membranes with devastating physiological consequences.

The interaction of viral peptides and their membrane milieus is difficult to characterize because of the complex interactions between peptides and membranes and within the membranes themselves. While these peptides can greatly influence membrane environments, the membrane environments themselves also impact the structure and function of peptides, and the interplay between peptides and membranes can depend on the membrane composition, temperature, pH, peptide sequence, and other factors. Thus in order to improve our understanding of important biological problems involving peptide–membrane interactions, particular systems must be studied as close to a biologically relevant context as possible.

Solid state nuclear magnetic resonance (ssNMR) is especially well suited to study membrane associated viral peptides. ssNMR can deliver atomic resolution information on structure and dynamics of peptides in near native environments; at the same time, ssNMR can also deliver complementary information on the membrane environment itself in under the same conditions, providing a more complete picture of peptide–membrane interactions. Fig. 1 provides an overview of information that can be obtained on viral membrane peptides and their bilayer environments and experiments described in this review. While this review focuses on ssNMR studies of viral peptide–membrane interactions, a number of other ssNMR studies just outside the scope of this review are worth mentioning, including studies of caveolin scaffolding domains [14], interaction of amyloid-forming proteins with lipid bilayers [15–21], antimicrobial peptides that interact with lipid bilayers [22,23], and the role of phospholipids in blood clotting [24]. This diverse array of membrane-interacting proteins highlights the unique ability of solid state NMR to acquire atomic level information on structure and dynamics of both the protein or peptide and the membrane environment itself and the important role ssNMR will play in providing deeper insight into disease mechanisms.

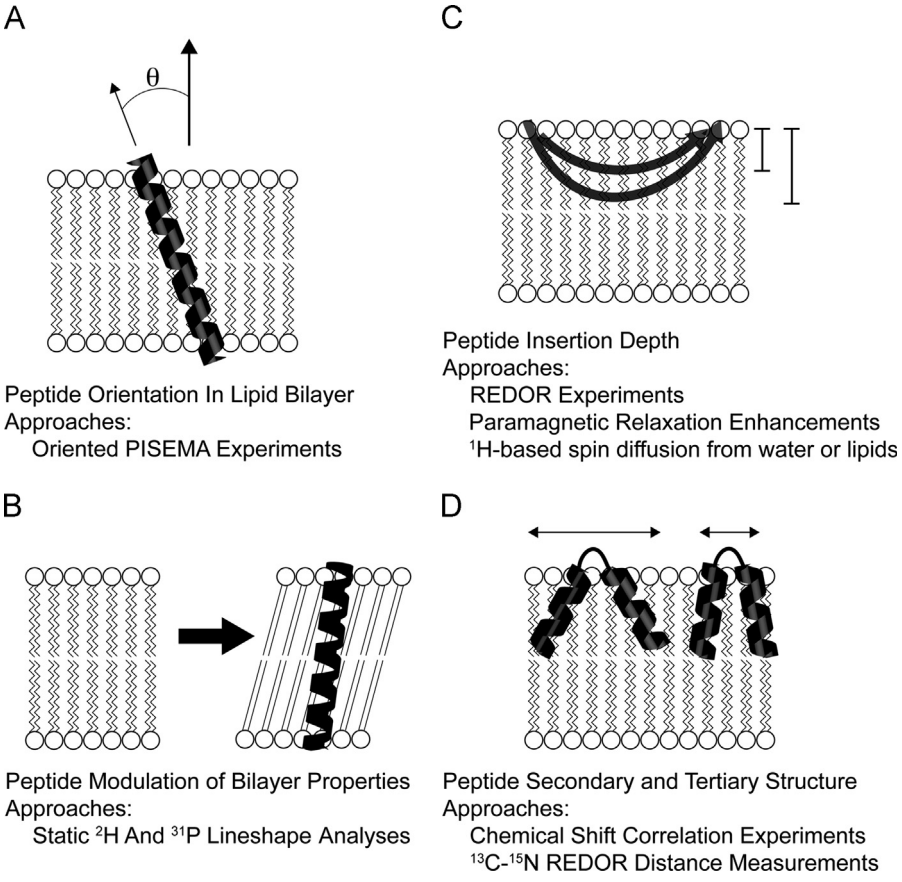

Fig. 1. An overview of information that can be obtained on viral membrane peptides and their bilayer environments and experiments are described in this review. (A) Peptide orientation in a lipid bilayer with respect to the membrane normal vector probed by PISEMA experiments; (B) properties of the lipid bilayer, including lipid phases, probed by experiments including analysis of ^{2}H and ^{31}P static line shapes; (C) insertion depth of peptides into lipid bilayers probed by REDOR experiments, PREs, and ^{1}H diffusion experiments transferring polarization from water or lipids to the peptide; (D) secondary and tertiary structures of peptides in lipid bilayers probed by analysis of secondary chemical shifts obtained from correlation experiments and ^{13}C–^{15}N REDOR distance measurements.

Please cite this article as: M.T. Eddy, T.-Y. Yu, Solid State Nucl. Magn. Reson. (2014), http://dx.doi.org/10.1016/j.ssnmr.2014.04.002