Biochimica et Biophysica Acta xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

The influence of cholesterol on membrane protein structure, function, and dynamics studied by molecular dynamics simulations ☆

Julie Grouleff, Sheeba Jem Irudayam, Katrine K. Skeby, Birgit Schiøtt *

Department of Chemistry and Interdisciplinary Nanoscience Center, Aarhus University, Langelandsgade 140, 8000 Aarhus C, Denmark

ARTICLE INFO

Article history:
Received 19 December 2014
Received in revised form 24 March 2015
Accepted 25 March 2015
Available online xxxx

Keywords:
Cholesterol
MD simulation
Membrane protein
Lipid–protein interaction
Amyloid peptide

ABSTRACT

The plasma membrane, which encapsulates human cells, is composed of a complex mixture of lipids and embedded proteins. Emerging knowledge points towards the lipids as having a regulating role in protein function. Furthermore, insight from protein crystallography has revealed several different types of lipids intimately bound to membrane proteins and peptides, hereby possibly pointing to a site of action for the observed regulation. Cholesterol is among the lipid membrane constituents most often observed to be co-crystallized with membrane proteins, and the cholesterol levels in cell membranes have been found to play an essential role in health and disease. Remarkably little is known about the mechanism of lipid regulation of membrane protein function in health as well as in disease. Herein, we review molecular dynamics simulation studies aimed at investigating the effect of cholesterol on membrane protein and peptide properties. This article is part of a Special Issue entitled: Lipid–protein interactions.

Contents

Abbreviations: AA, all-atom; AD, Alzheimer's disease; AFM, atomic force microscopy; BK channels, big potassium channels or large conductance, Ca^{2+}- and voltage-gated K^+ channels; CCM, cholesterol consensus motif; CG, coarse-grained; CRAC, cholesterol recognition/interaction amino acid consensus; CTD, cytosolic C tail domain; DMPC, 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine; DOPC, 1,2-dioleoyl-*sn*-glycero-3-phosphocholine; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; EM, electron microscopy; ErbB, epidermal growth factor receptor; FF, force field; $GABA_AR$, the γ-aminobutyric acid type A receptor; GluCl, glutamate-gated chloride channel; GPCR, G-protein coupled receptor; Kir, strongly inwardly rectifying K^+ channel; MD, molecular dynamics; MM/PBSA, Molecular Mechanics/Poisson–Boltzmann Surface Area; nAChR, the nicotinic acetylcholine receptor; NMR, nuclear magnetic resonance; PG, phosphatidylglycerol; POPC, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine; SERCA, the sarco/endoplasmic reticulum Ca^{2+}-ATPase; TEM, transmission electron microscopy; VDAC, the mitochondrial voltage-dependent anion channel.

☆ This article is part of a Special Issue entitled: Lipid–protein interactions.

* Corresponding author. Tel.: +45 87155975.
E-mail address: birgit@chem.au.dk (B. Schiøtt).

http://dx.doi.org/10.1016/j.bbamem.2015.03.029
0005-2736/

1. Introduction

One of the main challenges in structural biology is to understand the interplay between proteins and molecular constituents of the plasma membrane [1]. Lipid membranes encapsulate cells separating their interior from the extracellular matrix. The lipid bilayer is a complex mixture of phospholipids [2], glycolipids [3], and cholesterol arranged into two asymmetric leaflets [4]. The cholesterol present in cell membranes has been shown to be important for maintaining a healthy body, e.g., in regulating neurotransmission [5], cell signaling [6], and protein sorting [7,8]. An imbalance in the cholesterol level has similarly been implicated in many diseases, such as cancer [9], diabetes mellitus type 2 [10], and Alzheimer's disease (AD) [11,12] among others. However, a molecular understanding of how cholesterol is involved in these essential biochemical processes or how it may result in disease development is still lacking. Computational approaches applied to study how cholesterol influences the function of membrane-embedded proteins have added to the understanding of these processes and directed further experiments. This review provides a summary of these studies, with particular emphasis on molecular dynamics (MD) simulations and the insights they provide. Furthermore, an outlook into the future application of MD simulations to study interactions between cholesterol and various membrane components, focusing on how the function of the peptide and protein may be affected, is also included.

In this review, we aim to provide molecular-level insight into protein–cholesterol interactions and its effects on protein function. The review is divided into two parts. The first part provides an introduction to the cell membrane focusing on cholesterol, which includes a brief overview of regulation of membrane proteins and peptides by the lipid environment. Experimentally, such regulatory effects are extremely challenging to study, due to the dynamic nature of the cell membrane, which accordingly renders computational MD simulations very suitable for studying the effects of cholesterol on membrane proteins and peptides. We will conclude the first part with a short outline of how computational methods can assist in describing the effect of cholesterol on membrane proteins. The second part of the review highlights a number of studies in which MD simulations have shed light on membrane protein–cholesterol interactions. For the second part of the review, a comprehensive literature search was performed, and to the best of our knowledge it includes all studies in which the influence of cholesterol on the function of a membrane embedded protein or peptide has been studied using MD simulations. GPCRs are not included in the review rather the interested reader is referred to another contribution in this special issue [74].

1.1. Modulation of membrane proteins by the lipid environment

The cell membrane (or plasma membrane) separates the interior of a cell from the exterior, hereby protecting the cell. Membrane proteins encompass about 50% of the plasma membrane and are involved in many cellular processes, such as signaling across the membrane, cell–cell communication and the regulation of the access of nutrients and ions to and from the cell [13]. The last decade has provided increasing evidence that membrane lipids play important roles in shaping membrane–protein function [14]. Protein crystallography has further substantiated the importance of the lipid–protein interplay by reporting several structures with intimately bound lipids; cholesterol, cardiolipins, phosphatidylglycerol (PG) lipids, etc. have been found co-crystallized with both α-helical and β-barrel membrane proteins, prompting the question of how these lipids are influencing structure, function, and dynamics of membrane proteins [15]. Specifically, structures of proteins with co-crystallized cholesterol have been published over the past few years, including G-protein coupled receptors (GPCRs) [15], and most recently also transporters [16–18].

Recent research has revealed the existence of organization in the plasma membrane, such as the presence of highly ordered, cholesterol-enriched lipid raft microdomains [19,20]. Evidence also shows that some proteins are prone to segregate into these microdomains [19]. The relevance of such microdomains in the membrane, and their role in modulation of embedded membrane proteins is still much debated [21], though they are believed to be essential for many biological processes [22] including neurotransmission [23,24] and amyloid diseases [25]. The presence of integral membrane proteins also modulates the dynamics of the lipid environment. The lipids in the first ring surrounding the protein, referred to as the annulus, have a constrained motional freedom due to their interactions with the

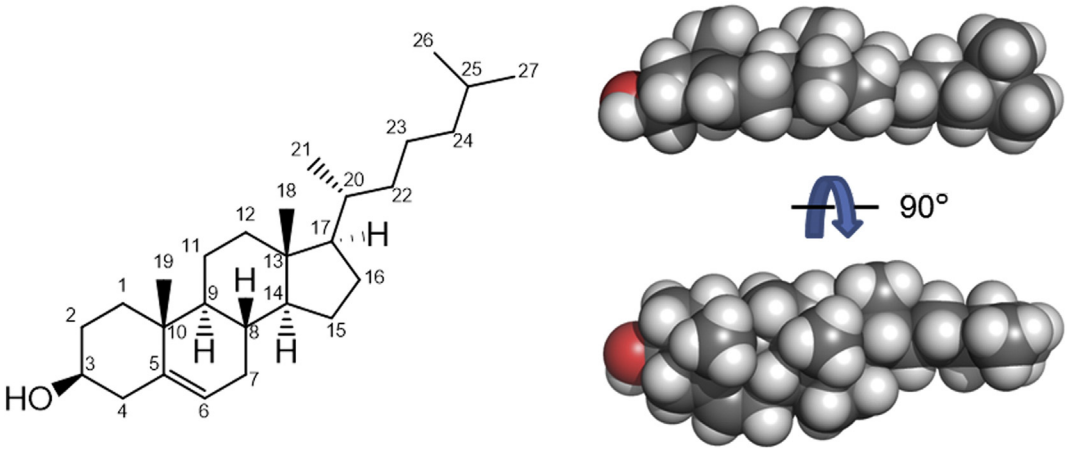

Fig. 1. The molecular structure of cholesterol.

Please cite this article as: J. Grouleff, et al., The influence of cholesterol on membrane protein structure, function, and dynamics studied by molecular dynamics simulations, Biochim. Biophys. Acta (2015), http://dx.doi.org/10.1016/j.bbamem.2015.03.029