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Influence of lipids on protein-mediated transmembrane transport

Elizabeth J. Denning[a], Oliver Beckstein[b,*]

[a] Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, United States
[b] Arizona State University, Center for Biological Physics, Tempe, United States

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Abbreviations:
PC, phosphatidylcholine
PE, phophatidylethanolamine
PS, phophatidylserine
PI, phosphatidylinositol
PG, phosphatidylglycerol
PA, phosphatidic acid
CL, cardiolipin
DPG, diphosphatidylglycerol
PIP_2 or $PI(4,5)P_2$, phosphatidylinositol 4,5-bisphosphate
SM, sphingomyelin
EPR, electron paramagnetic resonance
MFS, major facilitator superfamily
MD, molecular dynamics
TCDB, transporter classification database
PDB, protein databank

Keywords:
Membrane
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Transporter

ABSTRACT

Transmembrane proteins are responsible for transporting ions and small molecules across the hydrophobic region of the cell membrane. We are reviewing the evidence for regulation of these transport processes by interactions with the lipids of the membrane. We focus on ion channels, including potassium channels, mechanosensitive and pentameric ligand gated ion channels, and active transporters, including pumps, sodium or proton driven secondary transporters and ABC transporters. For ion channels it has been convincingly shown that specific lipid–protein interactions can directly affect their function. In some cases, a combined approach of molecular and structural biology together with computer simulations has revealed the molecular mechanisms. There are also many transporters whose activity depends on lipids but understanding of the molecular mechanisms is only beginning.

1. Introduction

Transport of ions and small molecules across the cell membrane is catalyzed by specialized proteins. Since transmembrane proteins are located within a lipid environment it is an obvious question in how far their function is dependent on or modulated by protein–lipid interactions. Are there any interactions essential to molecular transport beyond simply providing a stabilizing environment for the membrane protein? If so, what is the nature and specificity of these interactions? Are the physical thermo-elastic properties of the membrane sufficient to describe any effects or is a molecular detailed, chemical picture needed? As with many questions in biology, the answer seems to be "all of the above". In this review we set out to gather the evidence for the influence of lipids on the function of channels and transporters. We focus on the transport of matter by ion channels, water pores and primary and secondary transporters and regrettably omit the whole field of transmembrane signaling, i.e. the transport of information. Within the channels and transporters we are taking a broad view and try to gather a range of proteins for which functional experimental data suggests a direct effect of lipid type or bilayer properties on transport; for systems not included the reader is referred to other reviews (Opekarova and Tanner, 2003; Lee, 2004, 2011; Nyholm et al., 2007; Marsh, 2008). Unlike the situation a few years ago, we now also have crystal structures for many of the proteins themselves or for homologs and hence it is now becoming possible to develop a molecular picture of the effect of lipids on transmembrane transport.

* Corresponding author. Tel.: +1 480 727 9765.
E-mail addresses: denniej0@outerbanks.umaryland.edu (E.J. Denning), oliver.beckstein@asu.edu (O. Beckstein).

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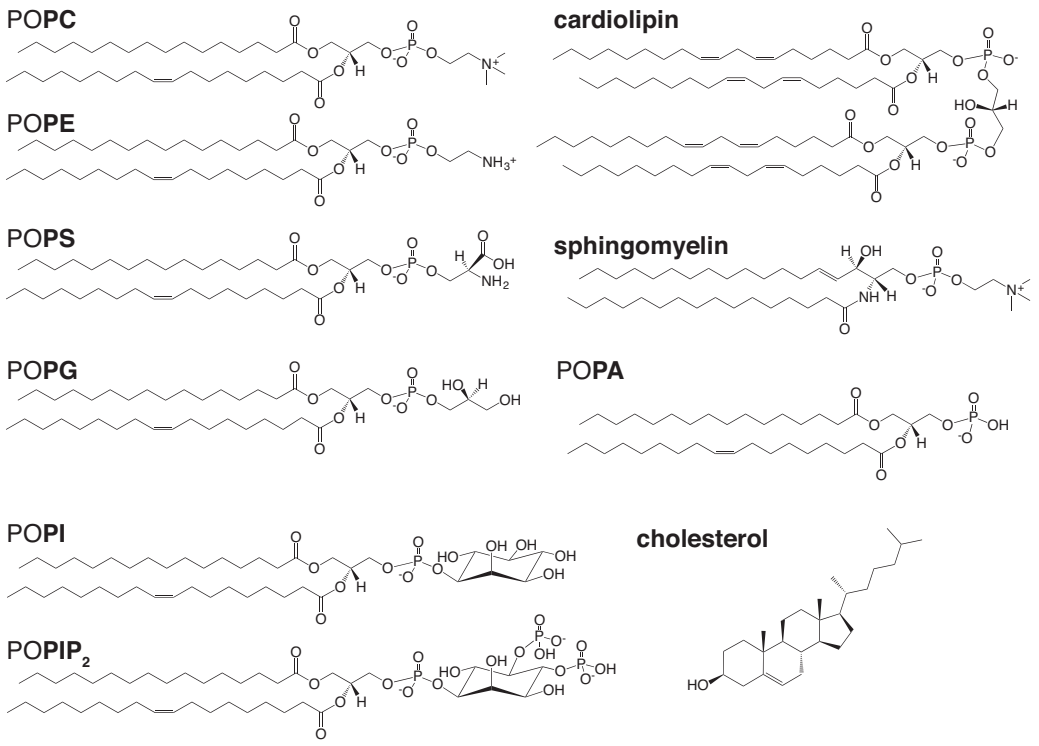

Fig. 1. Common types of lipids in biological membranes. A range of phospholipids are shown with the glycerol group acylated with a palmitoyl (16:0, abbreviated as P) and oleoyl (18:1(9Z), O) group in the sn1 and sn2 position. The headgroups are abbreviated as PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PIP_2, phosphatidylinositol 4,5-bisphosphate; PA, phosphatidic acid.

2. Biological membranes

Biological membranes contain membrane proteins and lipids. Polar (amphipathic) lipids consist of a hydrophilic headgroup and a hydrophobic tail region (van Meer et al., 2008). Most membrane lipids have a zwitterionic or charged headgroup, which largely determines the chemical properties (such as hydrogen bonding capability and charge) and hydrophobic acyl chains, which differ in length and the number of unsaturated bonds. Membrane properties such as the phase and fluidity depend on the balance between acyl chain packing and headgroup interactions. In aqueous solution, many lipid can assemble into membranous structures. Not all lipids can form bilayers, though; membranes in biological systems consist of mixtures of bilayer-forming lipids with other lipids.

The most common lipids found in biological membranes are glycerophospholipids, sphingolipids, sterols, and saccharolipids (classification according to LIPID MAPS (Fahy et al., 2005, 2009)). Glycerophospholipids consist of a glycerol backbone to which two acyl chains are attached at the sn-1 and sn-2 positions whereas a phosphate group is linked at sn-3. Fig. 1 shows zwitterionic (net-neutral under physiological conditions) phosphatidylethanolamine (PE) and phosphatidylcholine (PC), anionic phosphatidylserine (PS), phosphatidylinositol (PI), phosphatidylglycerol (PG), phosphatidic acid (PA), and the doubly phosphorylated PI, phosphatidylinositol 4,5-bisphosphate (PIP_2) with an overall charge of −3. Diphosphatidylglycerol, commonly referred to as cardiolipin (CL), is a charged lipid commonly found in prokaryotes and the inner membrane of mitochondria. Sphingolipids such as sphingomyelin (SM) are a major class of lipids in mammalian cells that can pack more tightly than PC and confer stability to a membrane (van Meer et al., 2008). Saccharolipids contain fatty acid directly linked to a sugar backbone. The outer membrane of Gram-negative bacteria consists predominantly of lipopolysaccharide (LPS), whose membrane component is the saccharolipid lipid A (Raetz et al., 2007).

Although this review focuses on the phospholipid component of the membrane it is worthwhile remembering that most eukaryotic membranes contain about 30–40% sterols such as cholesterol in addition to neutral and charged phospholipids. Sterols on their own do not form bilayers but together with bilayer-forming lipids, they can form a liquid-ordered phase (L_o or l_o) (van Meer et al., 2008). Addition of cholesterol to a pure lipid membrane above the liquid-crystalline phase transition temperature disrupts the liquid crystal so that the reduction in fluidity leads increased membrane stiffness. It also increases acyl chain ordering, which leads to membrane thickening above the phase transition temperature and membrane thinning below (Ipsen et al., 1990). The saturation of the lipid acyl chains can change this behavior and hence in general, cholesterol effects have to be assessed carefully in each case (Nomura et al., 2012).

2.1. Membrane composition

All organisms strive to keep their membranes in the liquid-crystalline L_α phase (also known as liquid-disordered L_d or l_d). Below a critical temperature, bilayers form a solid gel phase (L_β or s_o), which does not allow free lateral movement in the plane of the membrane. The transition temperature depends on the type of lipid, the length and saturation of the acyl chains, and the composition of the membrane (van Meer et al., 2008).

The phospholipid composition of some typical membranes are shown in Table 1 (see also e.g. Yorek, 1993; Opekarova and Tanner, 2003 and the Membrane Protein Lipid Composition Atlas (http://opm.phar.umich.edu/atlas.php) for more membranes of different species, organelles and tissues). Bacterial membranes are often rich in PE and PG lipids and contain cardiolipin (CL), which otherwise is mostly found in the inner membrane of mitochondria.