Chapter 16
Hydrophobic Mismatch in Membranes: When the Tail Matters

Bhagyashree D. Rao, Sandeep Shrivastava, and Amitabha Chattopadhyay

Abstract Hydrophobic mismatch is a specific case of lipid-protein interaction that takes place when the hydrophobic thickness of the transmembrane region of a membrane protein does not match the hydrophobic thickness of the membrane in which it is localized. Depending on the type of mismatch (positive or negative), the responses of membrane lipids and proteins vary. Hydrophobic mismatch could lead to changes in membrane protein folding, conformation, oligomerization and activity due to adaptation (mismatch response) by lipids or proteins. Hydrophobic mismatch can be observed in peptides as well as in larger transmembrane proteins that traverse the membrane a number of times such as G protein-coupled receptors (GPCRs). We propose a model of GPCR activation *via* hydrophobic mismatch based on literature data. Hydrophobic mismatch could play a role in cellular sorting and trafficking due to the gradient of cholesterol present in cellular organelles which gives rise to a gradient of increasing bilayer thickness from the endoplasmic reticulum to Golgi to the plasma membrane. We envision that hydrophobic mismatch could be an important player in lipid-protein interactions in the complex cellular milieu.

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16.1 Lipid-Protein Interaction

Biological membranes are organized molecular assemblies held together due to the hydrophobic effect [1] and display large variations in their lipid and protein compositions. They offer individual identity to the cell and its organelles, and are involved in cell-cell communication. Membrane proteins are crucial since they carry out a number of vital processes in cells and cell membranes help in maintaining an optimum environment for their function. Contrary to earlier models [2], cellular membranes are often crowded [3, 4] with a high protein density (typically ~25,000 proteins/μm^2; [5]). This is particularly true for biological membranes that carry out important cellular functions. A consequence of such crowding is that lipid-protein interactions play a crucial role in maintaining the structure and function of biological membranes [6, 7]. A major part of membrane proteins is immersed in the lipid bilayer and this offers a chance to membrane lipids to interact with the proteins for optimum functioning. Variations in cell membrane lipid composition due to stress or stimuli could therefore alter lipid-protein interactions.

In most cases of lipid-protein interactions, the interaction is mainly between various residues of the protein and the headgroup of the lipid (the hydroxyl group in case of cholesterol-protein interactions). However, there is a particular type of lipid-protein interaction, where the tail of the lipid is more important in terms of interaction with the membrane protein or peptide (and therefore 'the tail matters!').

16.2 Hydrophobic Mismatch

The hydrophobic thickness of the membrane is a fundamental property that has a profound effect on transmembrane protein structure and function [8, 9]. Hydrophobic mismatch is a specific case of lipid-protein interaction that takes place when the hydrophobic thickness of the transmembrane region of a membrane protein does not match the unperturbed hydrophobic thickness of the membrane in which it resides (see Fig. 16.1). Hydrophobic mismatch could lead to changes in membrane protein folding, conformation, and activity [10–12]. Such mismatch has obvious energetic consequences due to the juxtaposition of energetically unfavorable regions of the membrane lipids and the protein. While many lipid-protein interactions involve interaction of specific residues of membrane proteins with specific lipid headgroups (such as negatively charged lipids), hydrophobic mismatch is dependent on the hydrophobic thickness of the membrane bilayer, specifically of the annular lipids and the hydrophobic surface of the protein in contact with the membrane lipids. Mismatch is therefore an interaction that causes local perturbations in the membrane and may be linked to lateral heterogeneity in the membrane [13, 14].

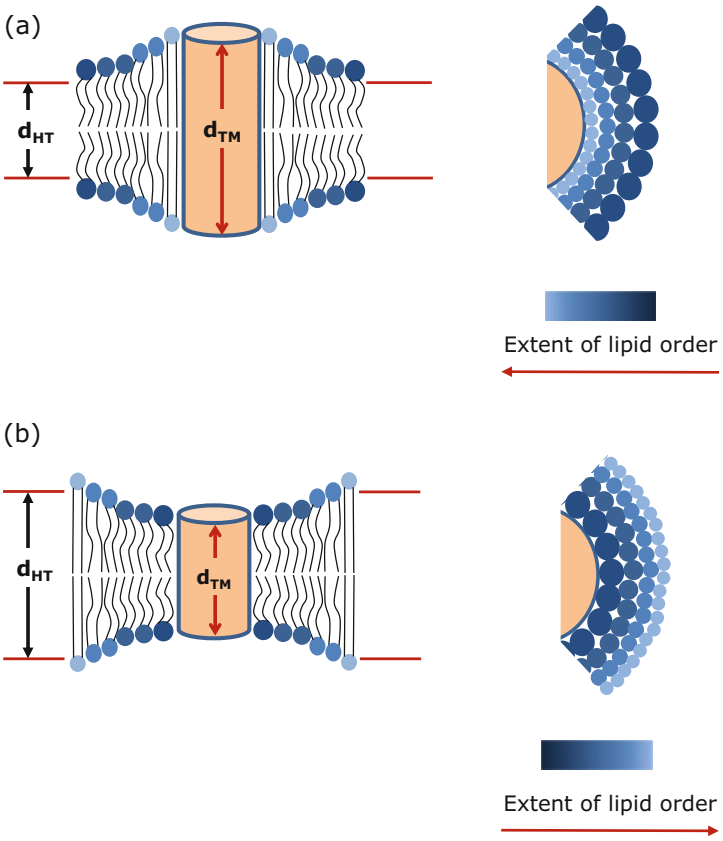

Fig. 16.1 A schematic representation of two types of hydrophobic mismatch and possible adaptations by membrane lipids. (**a**) A positive mismatch is induced when transmembrane domain length (d_{TM}) of the membrane protein is greater than the membrane bilayer hydrophobic thickness (d_{HT}). Under this condition ($d_{TM} > d_{HT}$), annular lipids surrounding the protein would get stretched to match the hydrophobic thickness of the transmembrane segment of the protein. This induces local ordering of lipid acyl chains in the vicinity of the protein and an increase in the phase transition temperature, leading to a reduction in the phospholipid headgroup area. The *top view* is shown at the *right*. (**b**) Negative mismatch results when the transmembrane domain length is shorter than the bilayer hydrophobic thickness (i.e., $d_{TM} < d_{HT}$). Negative mismatch induces local disorder in annular lipid chains, and a decrease in the phase transition temperature. This results in an increase in the phospholipid headgroup area. The *top view* is shown at the *right*

16.3 How to Determine Hydrophobic Thickness of Membranes and Membrane Proteins?

The extent of mismatch between the hydrophobic thickness of the membrane and the protein would determine the extent of the mismatch response [15]. A key concern is to experimentally estimate the hydrophobic thickness of membrane

proteins and the membrane bilayer. Determining membrane thickness is a non-trivial issue due to fluctuations of the membrane bilayer in addition to the inherent variations in available bilayer structural data [16]. One way to obtain hydrophobic thickness is from continuous X-ray scattering which measures the Gaussian distribution of the phosphate groups, and therefore the phosphate-to-phosphate distance [17]. The boundary of the hydrophobic thickness of the membrane is placed at the region where water ceases to be detected in the bilayer, i.e., at the *sn-2* carbonyl carbon [16, 18]. Hydrophobic thickness can therefore be obtained from the phosphate-to-phosphate distance by subtracting the thickness of the polar head group region, known from neutron diffraction of specifically deuterated samples to be 5.5 Å [19, 20]. Calculated this way, the hydrophobic thickness of pure fluid phase bilayers is found to vary linearly with acyl chain length [17]. This fluid phase thickness can be used to calculate the thickness of the gel phase by accounting for lipid tilt (∼30°) and increased thickness (∼30%) due to the all-*trans* acyl chain conformation in the gel phase [21]. However, such a calculation would give only approximate values for gel phase bilayers since average lipid tilt is known to be dependent on chain length [22].

The hydrophobic thickness of membrane proteins is more difficult to assess due to difficulty in obtaining high-resolution structures of membrane proteins. Hydrophobic thickness may be determined directly from crystal structures when the structure contains resolved lipid molecules that would mark the membrane interface [23]. In general, hydropathy profiles can provide an estimate of the number of residues in the transmembrane domain. The length of the hydrophobic (transmembrane) region can then be calculated assuming the transmembrane domain to be an α-helix, oriented parallel to the bilayer normal, with a vertical rise of 1.5 Å per residue. However, due to possible helical tilt, and contributions from the flanking residues, calculation of membrane protein thickness based on the length of the transmembrane domain may not always be straightforward. In addition, hydrophobic thickness of proteins has also been determined experimentally [24, 25].

16.4 Lipid and Protein Adaptation: Responses to Hydrophobic Mismatch

Lipids and proteins adapt to two different types of hydrophobic mismatch (positive and negative) in a number of ways. A positive mismatch occurs when the transmembrane domain length (d_{TM}) of the membrane protein is more than the membrane bilayer hydrophobic thickness (d_{HT}). When $d_{TM} > d_{HT}$, annular lipids surrounding the protein would get extended to match the hydrophobic thickness of the transmembrane domain of the protein (see Fig. 16.1a). This induces local ordering of annular lipid acyl chains resulting in an increase in the phase transition temperature, and a decrease in the phospholipid headgroup area (see Fig. 16.1a). The second kind of mismatch, i.e., negative mismatch, takes place when the

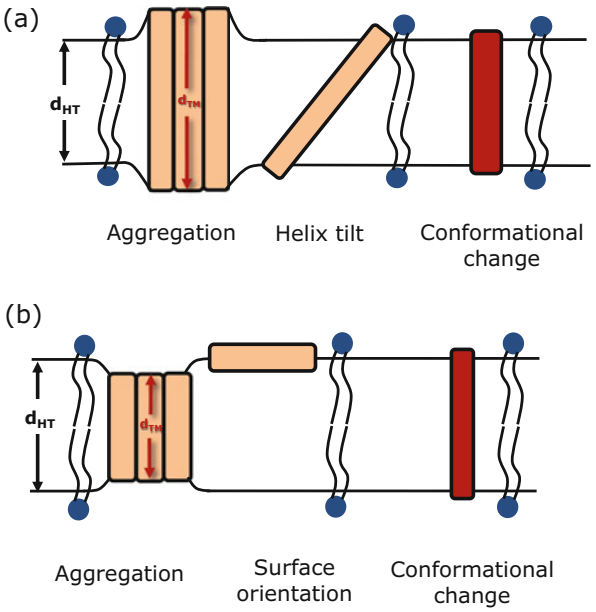

Fig. 16.2 A schematic representation of the possible adaptations of transmembrane proteins to hydrophobic mismatch. (**a**) Various adaptations of the protein upon positive mismatch (i.e., $d_{TM} > d_{HT}$). These include protein aggregation, tilting of transmembrane helices and conformational changes (shown in a different color) of the protein. (**b**) Under conditions of negative mismatch (i.e., $d_{TM} < d_{HT}$), the protein could adapt by aggregation, surface orientation and conformational change (shown in a different color)

transmembrane domain length is shorter relative to the bilayer hydrophobic thickness (i.e., $d_{TM} < d_{HT}$). Negative mismatch causes compression and local disordering of annular lipid acyl chains, a reduction in the phase transition temperature and a concomitant increase in the phospholipid headgroup area (see Fig. 16.1b). On the other hand, there could be several possible adaptations of the protein in case of positive mismatch (i.e., when $d_{TM} > d_{HT}$) which include protein aggregation, tilting of transmembrane helices and conformational changes (see Fig. 16.2a). In case of negative mismatch (i.e., when $d_{TM} < d_{HT}$), possible responses of the protein could be lateral aggregation, surface orientation and conformational change (see Fig. 16.2b). In addition, hydrophobic mismatch is believed to play an important role in membrane protein insertion and folding [26].

16.5 Hydrophobic Mismatch Models

Adaptation to hydrophobic mismatch has previously been described using a comprehensive thermodynamic model termed as the 'mattress model' [27]. The main idea underlying the mattress model is that any alteration of the sharp melting phase transition temperature (T_m) of lipid bilayers by the inclusion of proteins is a direct consequence of adaptation to hydrophobic mismatch that would occur on either side of the phase transition (since phase transition involves a large change (~30%) in the hydrophobic thickness of the membrane; [21]). In this model, adaptation to hydrophobic mismatch is modeled as a change in thickness of the annular lipid ring

as a result of compression or stretching of acyl chains, which leads to a shift (ΔT) in the phase transition temperature, relative to the T_m of a pure lipid bilayer. The magnitude of this shift is related to the extent of the mismatch. Therefore, long proteins in a short bilayer would cause stretching of annular lipids resulting in a shift toward a more gel-like (ordered) phase, and an increase in T_m (see Fig. 16.1a). Short proteins in a long bilayer would lead to compression of annular lipids, shift toward a more fluid phase and a decrease in T_m (see Fig. 16.1b).

In another model, Fattal and Ben-Shaul [28] characterized lipid-protein interactions and perturbations due to mismatch in terms of lipid deformation free energy change (ΔF), represented as a sum of hydrophobic core (lipid chain) and interfacial contributions. Importantly, this model assumes that protein-induced deformations persist in the membrane plane from the lipid-protein interface over typically a few molecular diameters (see Fig. 16.1). The lipid deformation free energy change (ΔF) accounts for changes in lipid chain order at the lipid-protein interface. When the hydrophobic lengths of the membrane and protein are equal, $\Delta F > 0$ due to the loss of conformational entropy experienced by the lipid chains at the protein interface. In mismatch situations, when the protein is longer than the membrane, ΔF further increases due to the enhanced stretching of the lipid chains. On the other hand, when the protein is shorter than the membrane, conformational entropy increases due to compression, but ΔF increases due to an increase in interfacial free energy. Therefore, ΔF is at a minimum when the hydrophobic lengths of the protein and membrane are equal but is always positive.

It should however be noted that theoretical models treat transmembrane proteins as smooth, rigid cylindrical impurities in the bilayer without vertical flexibility, characterized only by cross sectional area and hydrophobic thickness [15]. At the lipid-protein interface, the protein is assumed to be a nearly planar, smooth hydrophobic wall. In addition, these models are only valid for proteins at the infinite dilution limit and therefore do not account for any possible protein-protein interactions (e.g., lateral aggregation). Importantly, theoretical models highlight membrane deformation as a vital consequence of mismatch. Membrane deformation is related to the material properties of the membrane, and is therefore dependent on membrane composition, specifically cholesterol content ([29]; see later).

16.6 Hydrophobic Mismatch in Peptides

We will highlight representative examples of hydrophobic mismatch in peptides, which have been extensively studied. Gramicidin is a peptide which forms prototypical ion channels specific for monovalent ions and has been studied extensively to chararcterize lipid-protein interactions [30]. Previous experiments have shown that gramicidin adopts non-channel conformations under conditions of hydrophobic mismatch and aggregates in thicker gel phase membranes [31]. Simulation studies support the results obtained and revealed that in extremely negative mismatched condition, bilayer thinning occurs and is accompanied by conversion of gramicidin

from channel to non-channel form [32]. It has been previously shown that a mismatch between the length of gramicidin and the lipid acyl chains could induce non-bilayer phase (such as the hexagonal II phase) in model membranes [33]. In another study, the affinity of the pore-forming cholesterol-dependent peptide Perfringolysin O was found to increase for ordered lipid domains by hydrophobic matching between transmembrane hydrophobic thickness and bilayer hydrophobic thickness [34].

The WALP family of peptides [35], contains a stretch of alternating Leu-Ala residues that form the hydrophobic core of the peptide and two Trp residues at both ends that act as membrane interfacial anchors. Trp-flanked WALP peptides form rigid α-helices in the membrane [36] and have proved to be useful to understand basic characteristics of mismatch adaptation [37, 38]. Interestingly, synthetic WALP peptides illustrate the role of anchoring residues in mismatch adaptation, due to specific interactions of amino acid side chains with the membrane interface. The mismatch response of peptides of equal transmembrane thickness (i.e., with the same number of residues in the hydrophobic core) has been shown to be dependent on the nature of the anchoring residues [39–41]. Trp-flanked WALP peptides induce a larger lipid response (i.e., acyl chain ordering) in shorter bilayers as compared to equivalent Lys-flanked (KALP) or Arg-flanked (RALP) peptides [40, 42] due to the 'snorkeling' effect.

16.7 Hydrophobic Mismatch in GPCRs: A Model for GPCR Activation

G protein-coupled receptors (GPCRs) are important signaling hubs that serve as key drug targets in all clinical areas [43, 44]. Hydrophobic mismatch not only affects peptide orientation and function, but recent reports show that it plays a key role in maintaining the structure and function of GPCRs. For example, NMR measurements have shown that increasing bilayer thickness favors formation of metarhodopsin II (MII, active conformation) while oligomerization favors metarhodopsin I (MI, inactive conformation) [45].

Integral membrane proteins such as GPCRs utilize oligomerization as a response to hydrophobic mismatch since this helps to prevent the exposure of specific residues. The dimerization of β_2-adrenergic receptor has been studied at different cholesterol concentrations and a modulation of the dimer interface was observed by increasing cholesterol concentration [46]. Interestingly, in case of the β_2-adrenergic receptor, the hydrophobic mismatch was observed to be higher in presence of cholesterol [7, 46].

An elegant model of GPCR activation could be envisaged based on results of Alves et al. [47] on hydrophobic mismatch of human delta opioid receptor (see Fig. 16.3). This is based on active state dependent partitioning of the receptor, i.e., preferential partitioning of the agonist bound delta opioid receptor to

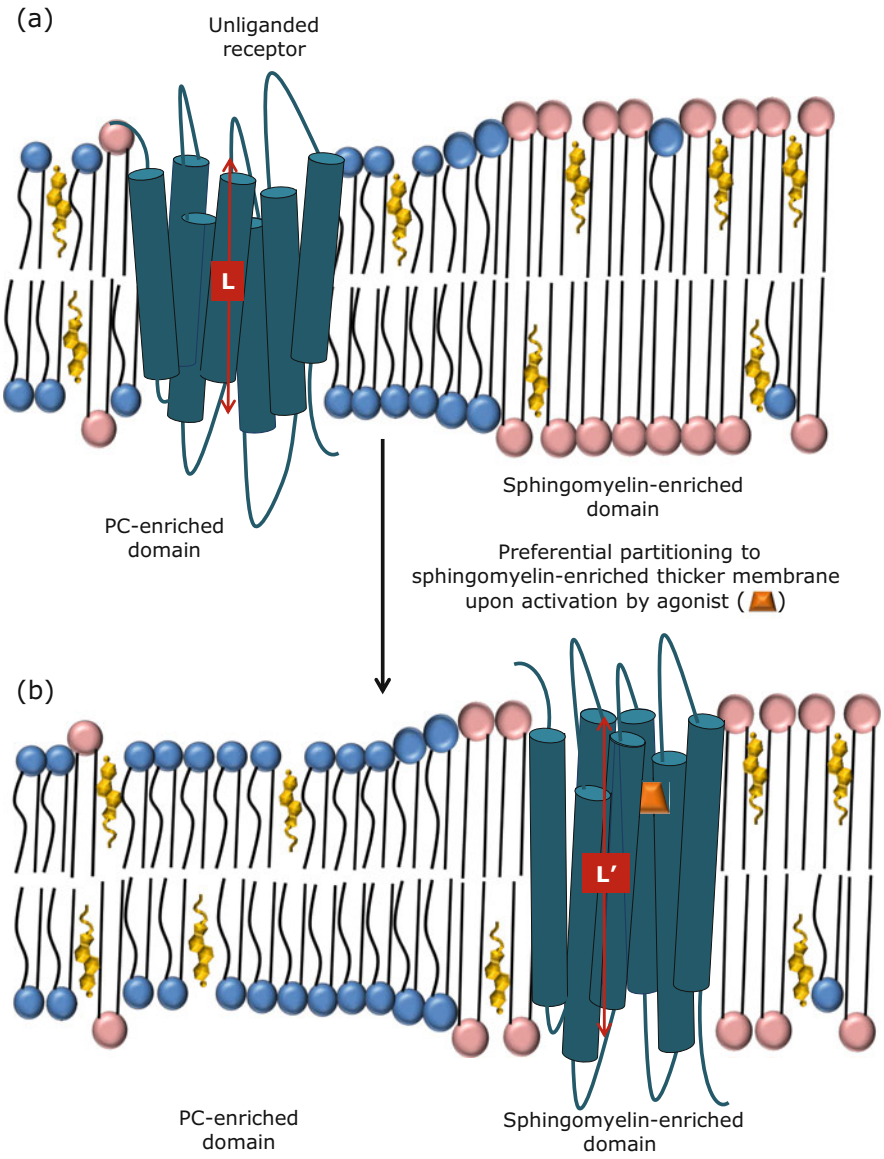

Fig. 16.3 Proposed model for activation of GPCR based on hydrophobic mismatch. (**a**) The receptor is localized in the shorter phosphatidylcholine (PC)-rich domain in the absence of ligand. (**b**) Upon activation by the agonist, the receptor undergoes conformational change such that the length of its transmembrane domain increases from L (unliganded state) to L′ (activated state). In response to the change in the transmembrane length of the receptor, the activated receptor is preferentially partitioned in the thicker sphingomyelin-rich domain due to favorable hydrophobic matching. This model is inspired from data reported in Alves et al. [47] on the human delta opioid receptor

sphingomyelin-rich thicker regions of the membrane due to elongation of its transmembrane domain upon activation by the ligand (see Fig. 16.3).

16.8 Is Hydrophobic Mismatch Relevant in Cell Membranes?

Cellular membranes display heterogeneity in thickness and composition due to the presence of a cholesterol gradient in various intracellular membranes. In eukaryotic cells, there is a gradient of increasing bilayer thickness from the endoplasmic reticulum to Golgi to the plasma membrane and all membrane proteins traverse this path. Hydrophobic mismatch has been proposed to play a crucial role in such sorting [48].

The endoplasmic reticulum is the site of cholesterol biosynthesis, yet interestingly has the lowest cholesterol content in membranes of the secretory pathway [48]. Cholesterol content increases gradually in the Golgi (along the *cis*-, *medial*-, and *trans*-Golgi stacks) with the plasma membrane having the highest concentration of cholesterol (∼90% of total cellular cholesterol). This cholesterol gradient could set up a possible thickness gradient along the biosynthetic pathway of membrane proteins since cholesterol is known to increase thickness of bilayers [49, 50]. This means that hydrophobic mismatch could occur if proteins specific to the Golgi, for example, gets mis-targeted to the plasma membrane. Interestingly, several studies have pointed out the importance of the transmembrane domain (TMD) in retention of proteins in the Golgi and ER [51–56]. Analysis from hydropathy plots showed that the average length of the TMD in Golgi proteins is ∼15 amino acids whereas the average length of the TMD in plasma membrane proteins is ∼20 amino acids [48, 51]. For example, replacing the TMD of a Golgi protein (sialyltransferase) by a hydrobhobic poly-Leu stretch of the same length results in its retention in the Golgi. However, when the length of the poly-Leu sequence was increased to ∼23 amino acids, the protein was expressed at the cell surface. This proves the significance of the length rather than sequence of the TMD to be the driving factor for sorting of proteins in cells [48, 51–53].

Long chain lipids and cholesterol often phase separate to form membrane domains of increased thickness in a complex membrane. Mismatched proteins could segregate to domains to relieve mismatch under such conditions. This type of membrane domains act as clustering hubs for mismatched proteins. Hydrophobic mismatch could lead to sorting of membrane proteins from cholesterol/sphingolipid rich domains of the Golgi to the plasma membrane. This hypothesis is further supported by the prediction that shorter proteins are efficiently excluded out of thicker cholesterol rich domains due to the high energetic penalty of deformation [57]. We should mention here that an alternate hypothesis, based on membrane thickness change along the exocytic pathway due to depletion of membrane proteins (rather than cholesterol content), has been reported [58].

16.9 Future Perspectives: What Lies Ahead

Biological membranes are complex, closely packed assemblies of lipids, proteins and carbohydrates. Work from a large number of groups over the years has shown the relevance of lipid-protein interactions in maintaining membrane structure and function. Most of these interactions involve the phospholipid headgroup with its various characteristics (size, shape, charge). In contrast, hydrophobic mismatch brings into focus the importance of the lipid acyl chains in lipid-protein interactions. In this review, we have highlighted the importance of hydrophobic mismatch in model and biological membranes with representative examples. Since membranes of eukaryotic cells contain thousands of diverse lipid types [59, 60], there could be further implications of hydrophobic mismatch that would encompass a broader area of cell biology. This will become apparent in years to come with advancements in lipidomics, proteomics and related approaches.

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