Review

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Biological membranes: the importance of molecular detail

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Are lipid interactions with membrane proteins best described in terms of the physical properties of the lipid bilayer or in terms of direct molecular interactions between particular lipid molecules and particular sites on a protein? A molecular interpretation is more challenging because it requires detailed knowledge of the 3D structure of a membrane protein, but recent studies have suggested that a molecular interpretation is necessary. Here, the idea is explored that lipid molecules modify the ways that transmembrane α-helices pack into bundles, by penetrating between the helices and by binding into clefts between the helices, and that these effects on helix packing will modulate the activity of a membrane protein.

Lipid- or protein-based approaches?

Our knowledge of membrane structure has grown greatly over recent years. We now have structures for many important classes of intrinsic membrane protein and we know much about the physical and structural properties of the lipid component of the membrane (Figure 1). How should this information be combined to provide a model for the biological membrane as a whole? In the literature, there are two broad approaches to understand how protein and lipid molecules interact in a membrane: lipid-based approaches and protein-based approaches. Lipid-based approaches emphasise the unusual material properties of the lipid bilayer, such as the gradients of mobility and order across the bilayer and the balance of tensions within the bilayer, and explore the possible importance of these properties for membrane protein function. Often molecular detail is ignored in these lipid-based approaches and the problem is cast in mechanical terms, such as the work required to distort a lipid bilayer around a membrane protein of simplified shape. The advantage of discarding molecular detail in this way is that it results in models that can be solved mathematically. In contrast, protein-based approaches generally concentrate on the molecular detail. A membrane protein is considered to be just another type of protein, and the aim is to see how far membrane protein function can be understood in terms of the types of interaction that are used to describe the functions of water-soluble proteins; only if an explanation could not be produced in conventional terms would some new effect, unique for membrane proteins, be introduced.

A number of recent reviews have described lipid-based approaches to membrane function [1–3]; the emphasis here will be on protein-based approaches.

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Solvation by lipid molecules

We are familiar with the idea that water-soluble proteins are covered by a layer of water molecules. Crystal structures of water-soluble proteins at low temperature show a first shell of water molecules making direct contact with the protein, and a second shell of water molecules that only make contact with other water molecules (Figure 2a) [4]. The water molecules in the first shell are perturbed by interaction with the protein and show dynamic properties different from those of bulk water [4]. The perturbation does not, however, extend very far from the protein surface; at a distance of about 7 Å, all the water molecules have bulk properties [5] and because the diameter of a water molecule is about 3 Å, this means the perturbation extends no further than the second shell of water molecules and will, of course, be most marked for the first shell [6].

A similar picture applies to solvation of an intrinsic membrane protein by lipid molecules, as first shown by electron paramagnetic resonance (EPR) studies with spin-labelled lipids [7]. The EPR spectrum obtained from a spin-labelled lipid in the presence of a membrane protein such as the Ca^{2+}-ATPase from muscle sarcoplasmic reticulum shows two components (Figure 2b, ii) [8]. One component represents lipid molecules with restricted mobility, corresponding to a first shell of lipid molecules interacting directly with the protein; the other component representing a mobile fraction of lipid molecules, with a mobility similar to that of bulk lipid (Figure 2b) [7,8]. The first shell of lipid molecules is often referred to as the lipid annulus, because it forms an annulus or ring around the protein [9]. This picture of lipid organization has now been confirmed by a variety of electron microscopy (EM) and X-ray diffraction studies that have shown some of the annular lipid molecules bound to a membrane protein surface, distorted by binding to the surface [10]. Figure 3 illustrates a number of such lipid molecules adopting highly distorted conformations on the surface of aquaporin [11]. This distortion can take a number of forms. Phospholipid headgroups of bound phospholipid molecules are not restricted to the bent-down conformation of the phosphodiester group characteristic of a phospholipid bilayer; conformations of the glycerol backbones for bound phospholipid molecules are not restricted to the gauche C1–C2 rotomers found in phospholipid bilayer crystals, and the fatty acyl chains adopt conformations on a protein surface very different from the average conformation, parallel to the bilayer normal, adopted in a fluid lipid bilayer [12].

The idea of a lipid annulus does not imply that individual lipid molecules spend a long time on the surface of the

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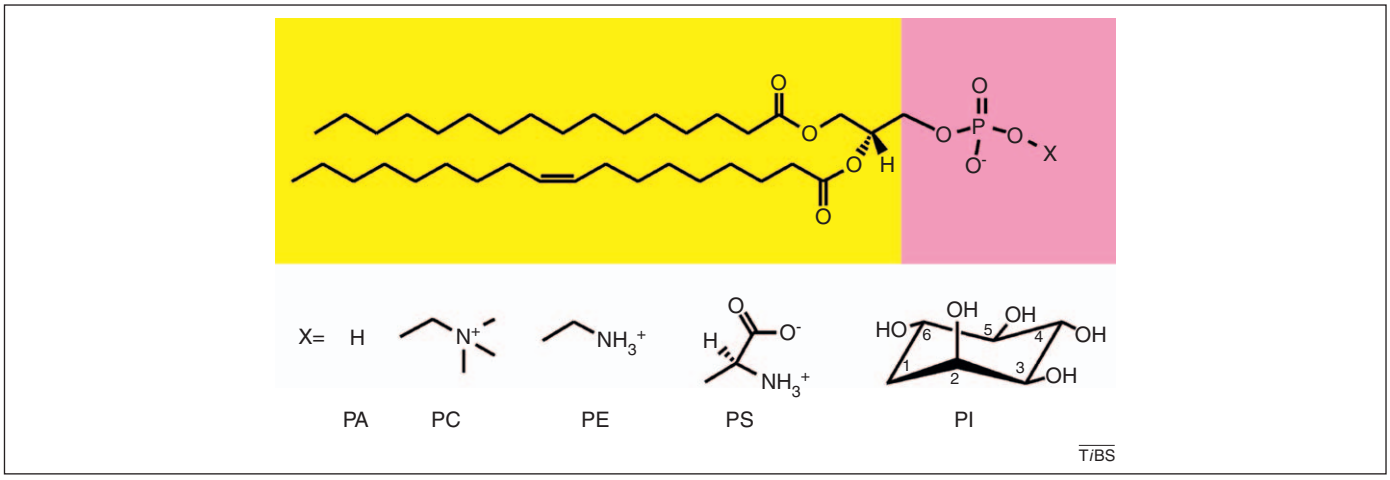

Figure 1. Lipid structures. The structures of the major glycerophospholipids phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS) and phosphatidylinositol (PI). Yellow indicates the hydrophobic tails of the lipids, and orange the lipid headgroup region that defines the charge on the lipid molecule, with either no net charge (PE and PC) or a net negative charge (PA, PS and PI).

protein. In the same way that most of the first shell water molecules around a water-soluble protein come on and off the surface at a fast rate, most of the lipid molecules in the annulus exchange rapidly with the bulk lipids in the membrane [8]. The rate of exchange between the lipid annulus and the bulk is generally around 1–2 $\times$ 10^7 s^{-1} at 37 °C; about a factor of two slower than the rate of exchange of two lipids in a fluid lipid bilayer [8,13]. Of course, fast exchange of lipid molecules does not actually matter for a membrane protein; a lipid molecule will become distorted as soon as it moves onto the surface of the protein and membrane proteins will, therefore, always be surrounded by a layer of distorted lipid molecules, whatever the rate of lipid exchange. Any selectivity in lipid binding would be expected to be reflected in a slow off-rate for the lipid leaving its binding site, although the on-rate could also be slow for a lipid molecule that had to penetrate into a deep cleft in the protein surface.

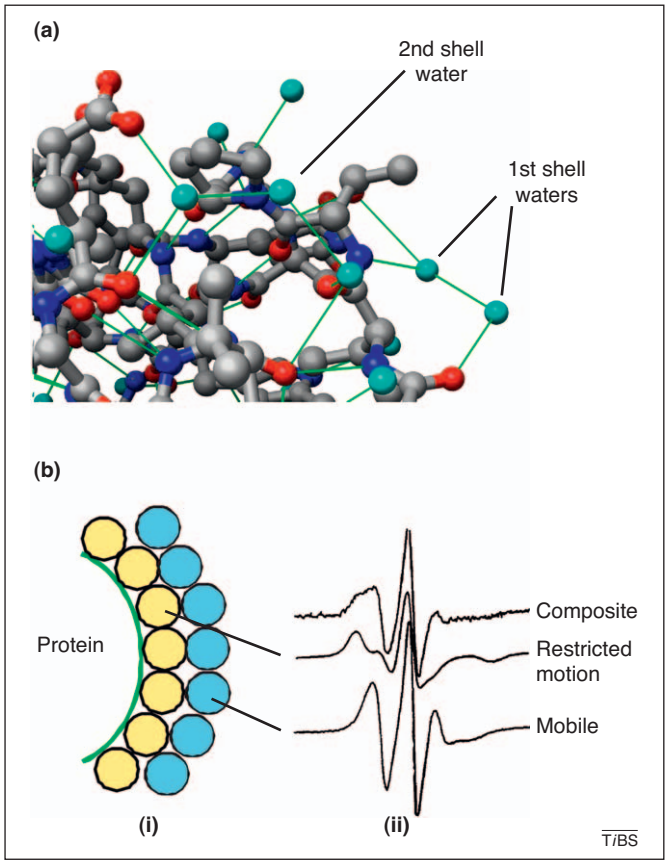

Figure 2. Solvation of a protein by water and lipid. **(a)** The surface of a water-soluble protein is covered by a first shell of water molecules making direct contact with the protein, and by a second shell of water molecules only making contact with other water molecules. Atoms are coloured red for acidic and dark blue for basic; water molecules are light blue. (Modified from an original by Matthew Cordes). **(b) (i)** A view of a membrane protein from the top, showing the first shell of lipid molecules (yellow) often referred to as the lipid annulus, and a second shell of lipid molecules (blue). **(ii)** EPR spectra for a spin-labelled lipid in the presence of Ca^{2+}-ATPase. The experimental spectrum is a composite made up of a component due to lipid with restricted motion (the annular lipid) and a mobile component due to lipid not in contact with the protein [8].

The fact that most lipid molecules are in fast exchange suggests that the interaction between a lipid molecule and the surface of a membrane protein is non-sticky. The protein surface is not covered with a series of deep energy wells into which the lipid molecules fall to give a single favoured conformation. Rather, the total interaction energy between a lipid and a protein molecule represents the sum of many weak van der Waals, hydrogen bonding and electrostatic interactions, and thus will fluctuate widely; lipid molecules are not frozen in single long-lived conformations on a protein surface. This is reflected in the fact that lipid molecules are rarely resolved in crystal structures of membrane proteins, even when lipid is known to be present. To that extent, the structures of the annular lipid molecules on the aquaporin surface shown in Figure 3 are non-representative; lipid headgroups and chains are well resolved in the aquaporin structure because aquaporin crystallizes as a tetramer with just a single shell of lipid molecules separating the tetramers; most of the lipid molecules will therefore be in contact with two protein surfaces not just one, restricting their possible freedom of motion.

The idea of relatively non-specific lipid–protein interactions in the lipid annulus has been confirmed by measuring lipid binding constants, using either EPR or fluorescence methods [13–16]. These measurements show that lipid binding constants generally vary only slightly with fatty acyl chain length or lipid headgroup. These slight differences in interaction could, however, be important for protein function because the local concentrations of lipid

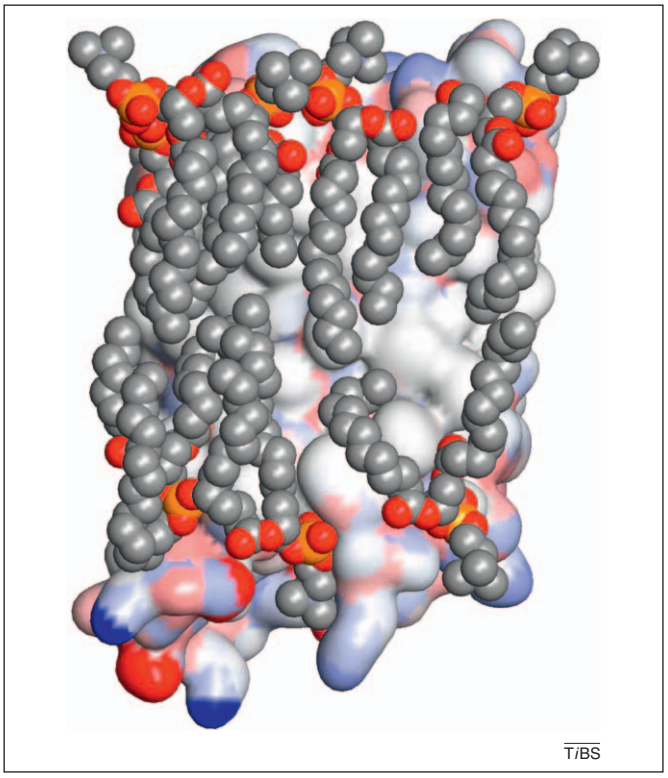

Figure 3. Bound lipid molecules. The surface of a membrane protein is covered by a bilayer of lipid molecules (the annular lipids), distorted to match the rough surface of the protein. Shown here are the annular lipid molecules bound on the surface of aquaporin. The lipids are shown in space-fill representation; the surface of the protein is shown coloured by atom charge, ranging from red for negative to blue for positive. Coordinates from PDB file 2B60.

molecules in a membrane are high. For example, the cytoplasmic membrane of *Escherichia coli* contains about 70% of the zwitterionic lipid phosphatidylethanolamine, and 24% and 4%, respectively, of the anionic lipids phosphatidylglycerol and cardiolipin [17]. With a molar ratio of lipid:membrane protein of the order of 100:1 [10], the mole fraction of cardiolipin in the membrane will be around 0.04, compared to a mole fraction of around 0.7 for the 'background' lipid, phosphatidylethanolamine. To put this into a more familiar context, 1 mM is considered a high concentration for a ligand in water, and a 1 mM solution in water corresponds to a mole fraction of ligand of 0.00005, compared to a mole fraction of water close to 1. This means that high ligand affinities are required at binding sites where binding of ligand is in competition with binding of water, but only a slightly higher affinity for cardiolipin compared to phosphatidylethanolamine would ensure that a lipid binding site were occupied by cardiolipin rather than phosphatidylethanolamine, even if the membrane contained only 4% cardiolipin.

An additional factor that needs to be considered is that many effects of annular lipids on a membrane protein are cooperative [3]. For example, the activity of the Ca^{2+}-ATPase from sarcoplasmic reticulum is lower in bilayers of phosphatidylethanolamine than in bilayers of phosphatidylcholine, but in mixtures of the two lipids, it is only when the phosphatidylethanolamine content exceeds 80% that ATPase activity drops [18]. Cooperativity arises because there are about 30 annular lipid binding sites around the Ca^{2+}-ATPase; although effects of lipid binding at just one of these sites will not be sufficient to cause a major change in the conformation of the Ca^{2+}-ATPase, the additive effects of binding at many of the sites will. The activities of the mechanosensitive channel of large conductance MscL [19], the multidrug transporter LmrP [20] and the metarhodopsin I to II equilibrium for rhodopsin [21] are also different in bilayers of phosphatidylcholine and phosphatidylethanolamine. Studies of the effects of lipids with intermediate levels of methylation in the headgroup have shown that these effects depend on whether the lipid headgroup can form hydrogen bonds with the protein [19–21].

As well as the structure of the lipid headgroup, the structures of the lipid fatty acyl chains are also important for membrane protein function [22]. In most natural phospholipids, at least one of the two chains is unsaturated, ensuring that the lipid will be in the fluid, liquid crystalline phase at physiological temperature. The length of the chain is also important because this will determine the thickness of the hydrophobic core of the lipid bilayer, which is expected to match the thickness of the membrane-spanning region of a membrane protein. The activity of the Ca^{2+}-ATPase for example, is highest in bilayers of lipids with chains in the length range of C16 to C20, with shorter or longer chains supporting low activities [22]. Small differences between the hydrophobic thicknesses of the lipid bilayer and the protein can be compensated for by minor stretching or compression of the lipid bilayer around the protein but large changes in bilayer thickness will lead to distortions of the protein structure, such as changes in the tilt angles for the transmembrane α-helices or local changes in side chain packing at the lipid–water interface, resulting in decreases in activity of the protein [22].

As well as these non-specific interactions of lipids with the bulk of the trans-membrane surface of a membrane protein, a few 'hot-spots' have been detected where particular classes of lipid bind with higher specificity. For example, a cluster of three positively charged residues is located on the cytoplasmic side of MscL in a position to interact with the headgroup of a negatively charged lipid (Figure 4a); phosphatidic acid has been shown to bind to this region of MscL with an affinity about nine times that of phosphatidylcholine, modifying MscL function [15,23]. A similar positively charged cluster is seen in the potassium channel Kir2.2 (Figure 4b) and binding of anionic lipids such as PtdIns(4,5)P2 to this cluster modulates channel function [24]. Again, a charged cluster, this time of four residues, is located on the plasma membrane Ca^{2+}-ATPase close to the lipid–water interface where the anionic lipid molecules important in pump activation can bind [25].

Buried lipids

As well as the annular lipid molecules interacting with the bilayer-exposed surface of a membrane protein, lipid molecules are sometimes found buried within a membrane protein; these lipids have been referred to as non-annular lipids to distinguish them from the lipids bound to the annular sites [26]. Buried lipid molecules generally make some contact with the annular lipids, even if they are bound in deep grooves in the protein surface, and the

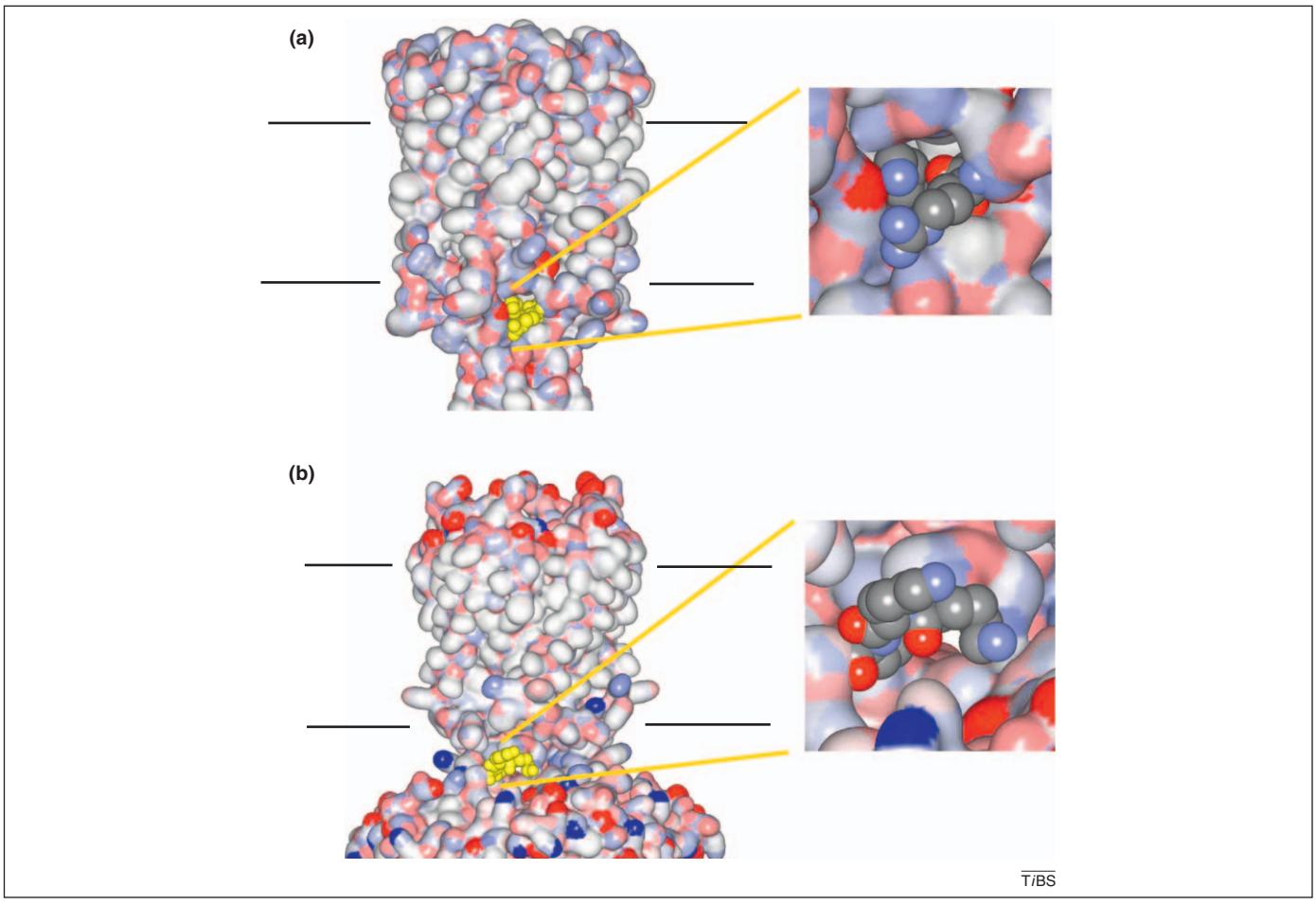

Figure 4. Charge clusters in the lipid annulus. Clusters of positively charged residues are found in some membrane proteins in a position to interact with the headgroups of negatively charged lipid molecules. Two clusters of three positively charged residues are shown in space-fill representation coloured yellow for **(a)** MscL (Arg98, Lys99 and Lys100) and **(b)** for Kir2.2 (Lys188, Lys189 and Arg109); the rest of the protein being shown as a surface coloured by atom charge. The horizontal lines show the approximate positions of the hydrophobic core of the surrounding lipid bilayer. The pictures on the right show the charge clusters at higher magnification, with normal colouring. Coordinates from PDB files 1MSL and 3JYC. For MscL the side chain of Lys100 has been modelled in.

headgroups of the buried lipids are generally located in the same plain as the headgroups of the lipids in the bulk lipid bilayer [10], suggesting that the buried lipids incorporate into their binding sites by simple diffusion from the bilayer. An example is provided by the phosphatidylglycerol molecule resolved in the crystal structure of the heterotrimeric nitrate reductase A (Figure 5a) [27]. Only the first seven and four carbons respectively of the two fatty acyl chains are resolved, but the lipid headgroup is well resolved. The headgroup is bound in a pocket formed by all three subunits with a number of positively charged residues contributing to the binding site (Figure 5a). With major contributions to the binding site coming from two subunits that are not transmembranous, the headgroup binding site resembles that on an extrinsic membrane protein binding to the surface of a membrane. Although the effect of phosphatidylglycerol on the function of nitrate reductase A appears not to have been defined, it is likely that it plays a major structural role, holding the heterotrimeric structure together.

In the case of the potassium channel KcsA, a functional role has been demonstrated for the anionic lipid molecules bound at protein–protein interfaces in the homotetrameric structure (Figure 5b) [28]; the open probability for the channel is low in the absence of anionic lipid, probably through effects of anionic lipid on the selectivity filter of the channel, reducing the level of C-type inactivation [29].

Lipids play a particularly important role in the multisubunit complexes involved in bioenergetics. For example, 13 lipid molecules have been resolved in the crystal structure of cytochrome oxidase, two cardiolipins, one phosphatidylcholine, three phosphatidylethanolamines, four phosphatidylglycerols and three triglycerides, each binding to their own specific sites [30]. Four of the non-annular lipid molecules in cytochrome oxidase are important in homodimer formation; the lipid fatty acyl chains playing a space-filling role at the interface [30]. Equally impressive are the complexes involved in photosynthesis [31]. Twenty-five lipid molecules have been resolved in the crystal structure of the homodimeric cyanobacterial photosytem II complex, 11 monogalactosyl diacylglycerols, seven digalactosyl diacylglycerols, five sulfoquinovosyl diacylglycerols, and two phosphatidylglycerols [32]. There are relatively few protein–protein contacts at the monomer–monomer interface in the dimeric structure and 14 of these lipid molecules, seven from each monomer, fill space at the

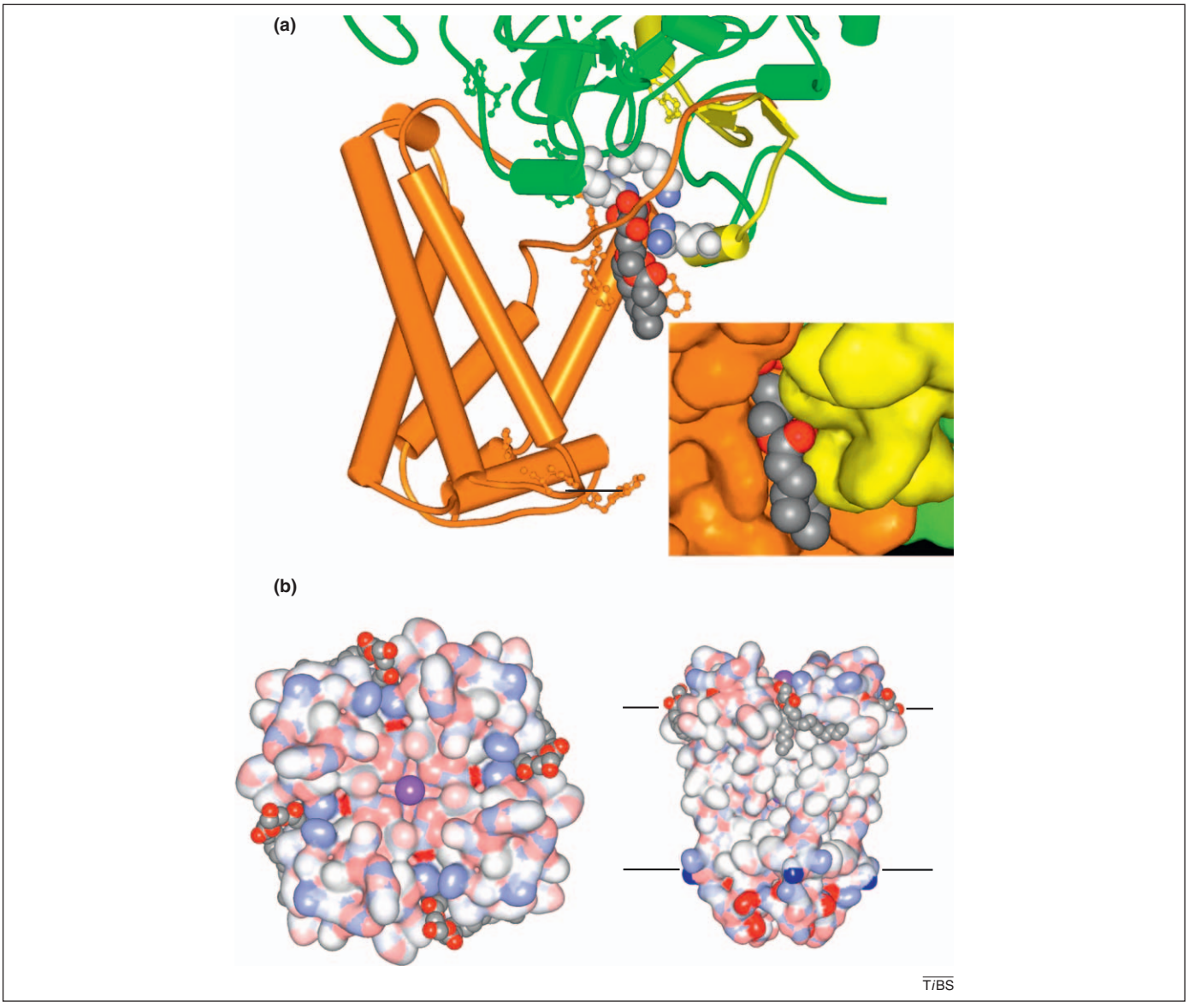

Figure 5. Buried lipid molecules. Shown here are two examples of lipid molecules buried within the structure of a membrane protein. **(a)** The heterotrimer of nitrate reductase A. The subunits NarG, NarH and NarI are coloured yellow, green and brown, respectively. Trp residues are shown in ball-and-stick representation and the bound phosphatidylglycerol (PG) molecule is shown in space-fill representation. Charged residues Arg6 in NarG and Lys216 and Arg218 in NarH that contribute to the binding of the PG molecule are also shown in space-fill representation. The insert shows how PG binds between the surfaces of the three monomers making up the heterotrimeric structure. Coordinates from PDB file 1Q16. **(b)** PG molecules bound at protein–protein interfaces in the homotetrameric KcsA structure shown in space-fill representation, in a view (left) from the extracellular side of the membrane and (right) a side view with the approximate position of the hydrophobic core of the bilayer shown by the horizontal lines. A potassium ion (purple) moving through the central pore is shown in the centre of the view on the left. Coordinates from PDB file 1K4C.

interface, together with chlorophylls and carotenoids. Of the remaining lipids, eight form a 'bilayer island' encircled by protein subunits where the exchange occurs between reduced plastoquinone and fresh plastoquinone from the plastoquinone pool in the thylakoid membrane [32]. Particularly interesting is the presence of molecules of both monogalactosyl diacylglycerol and digalactosyl diacylglycerol in the structure. Monogalactosyl diacylglycerols with unsaturated chains prefer, on their own, to form non-bilayer, curved structures, whereas digalactosyl diacylglycerols, with their larger headgroups, form normal bilayers, but the roles of these lipids in the photosystem II structure are clearly unrelated to these packing preferences and, instead, depend on interactions between the lipid headgroups and their binding sites in the protein. Photosystem I is also rich in essential lipid molecules, with three buried phosphatidylglycerol molecules and one buried monogalactosyl diglyceride being resolved per photosystem I monomer in the cyanobacterial structure [31].

A study of the photosynthetic reaction centre from *Rhodobacter sphaeroides* has shown the presence of a specifically bound cardiolipin molecule and the presence of grooves on the membrane-spanning surface of the protein to which a variety of phospholipid molecules with different headgroup structures can bind [33]. This idea of lipid molecules binding in grooves between transmembrane α-helices has emerged as an important aspect of lipid–protein interactions. Many membrane proteins contain bundles of transmembrane α-helices and the functions of such proteins involve subtle movements of individual helices within the helix bundle, such as tilting, bending, or unwinding, rather than uniform changes to the whole

bundle such as changes in its diameter or thickness. In some cases, proper packing of a set of helices requires the presence of lipid molecules between the helices simply to fill space between the helices. A molecular dynamics simulation of the interaction of rhodopsin with lipids containing polyunsaturated fatty acyl chains has shown the chains penetrating deeply into the protein core, modifying helix–helix interactions [34]. If a membrane protein contains loops running along the membrane surface, lipid molecules will also be required to fill the space below the loops. This has been demonstrated for rhomboid protease [35]. Here, two lipid molecules have been resolved filling a hydrophobic cavity formed by a combination of a loop lying parallel to the membrane surface and a gap between two of the transmembrane α-helices.

There is growing evidence for the functional importance of this packing role of lipid molecules. In the Ca^{2+}-ATPase, a molecule of phosphatidylethanolamine has been observed bound in a cavity between transmembrane α-helices M2 and M4 in the Ca^{2+}-free conformation of the protein, acting as a wedge keeping these helices apart [36]. In the Ca^{2+}-bound form of the ATPase, the cavity between M2 and M4 is closed so that the phosphatidylethanolamine molecule must be displaced on binding Ca^{2+} [36], providing a possible explanation for some of the effects of phosphatidylethanolamine on Ca^{2+}-ATPase function [18]. A similar example is provided by the effect of the hydrophobic inhibitor of the Ca^{2+}-ATPase, thapsigargin [37,38]. Thapsigargin binds to the Ca^{2+}-free ATPase in a lipid-facing cavity formed by helices M3, M5 and M7 (Figure 6a). Binding of Ca^{2+} to the ATPase results in helices M3 and M7 moving closer together, closing the cleft; binding of thapsigargin and Ca^{2+} is therefore competitive, explaining why thapsigargin is an inhibitor of the Ca^{2+}-ATPase. Other hydrophobic inhibitors of the Ca^{2+}-ATPase such as *t*-butyl-hydroquinone and cyclopiazonic acid work in an analogous fashion, binding to specific cavities between the transmembrane helices, blocking helix movement [38]. Binding of drugs and other small amphipathic molecules in clefts and cavities has now been demonstrated for a range of membrane proteins (Box 1).

Cholesterol

Another molecule that has now been shown to interact directly with membrane proteins is cholesterol [39]. Cholesterol is a major component of the outer membranes of mammalian cells, making up about half of the lipid molecules. As a result of its relatively rigid structure, cholesterol decreases the mobility of phospholipid fatty acyl chains and, at one time, it seemed reasonable to suppose that these effects on the mechanical properties of the bilayer could provide an explanation for the effects of cholesterol on the function of many membrane proteins.

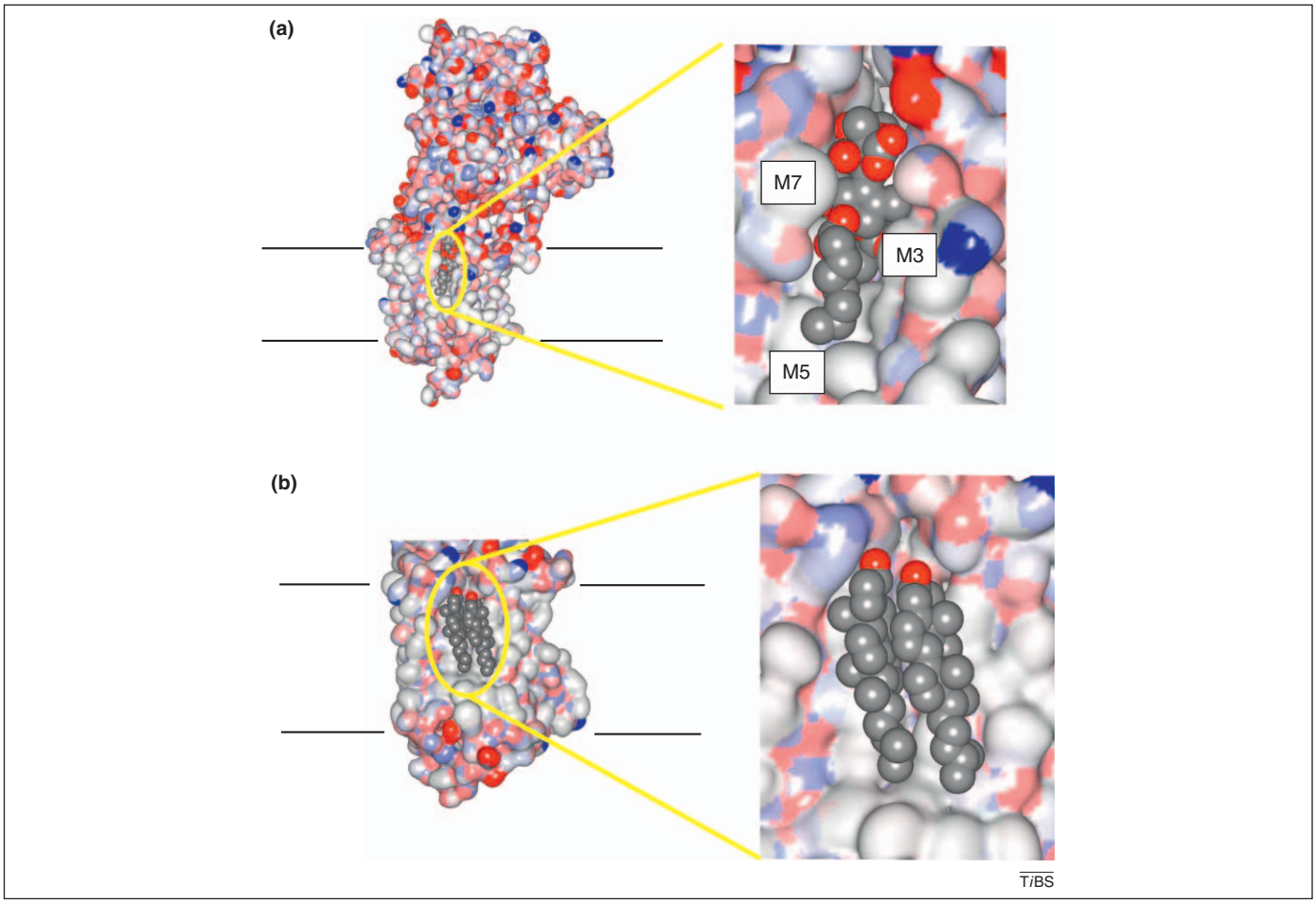

Figure 6. Amphipathic molecules other than phospholipids can bind in clefts between transmembrane α-helices. **(a)** Left, the inhibitor thapsigargin bound to the Ca^{2+}-ATPase is shown in space-fill representation, circled in yellow. Right, an expanded view of the binding site, located in a cleft between transmembrane α-helices M3, M5 and M7. Coordinates from PDB file 1IWO. **(b)** Left, two cholesterol molecules bound to the β_2-adrenergic receptor are shown in space-fill representation, circled in yellow. Right, an expanded view of the binding site, again in a cleft on the surface. Coordinates from PDB file 3D4S.

Box 1. Effects of small amphipathic molecules on membrane proteins

It was long thought that small amphipathic molecules such as drugs and fatty acids could affect membrane protein function indirectly through effects on the mechanical properties of the lipid bilayer component of a membrane [46]. However, there are now several examples where direct interaction of such molecules with membrane proteins has been established.

Ca^{2+}-ATPase: inhibitors such as thapsigargin and *t*-butylhydroquinone bind in clefts and cavities between transmembrane α-helices (Figure 6a) [37,38].

(Na^+-K^+)-ATPase: the inhibitor ouabain binds deeply inserted into a cleft between transmembrane α-helices [47].

K^+-channels: tetraalkylammonium ions, models for local anaesthetics such as lidocaine, and fatty acids bind to a hydrophobic, water-filled cavity in the channel to block it [48,49].

Pentameric ligand-gated ion channels: the general anaesthetic molecules, propofol and desflurane bind in a cavity between the transmembrane α-helices, accessible from the lipid bilayer [50].

However, it now seems more probable that many of the observed effects follow from direct interactions with the protein. A few examples will suffice. Cholesterol affects ligand binding to many G protein-coupled receptors and increases their thermal stability. A crystal structure of the β_2-adrenergic receptor shows a pair of cholesterol molecules bound in a cleft whose side is made up of helices I and IV, and whose back is made up of helices II and III (Figure 6b) [40]. A molecular dynamics simulation of the A_{2A}-adenosine receptor has suggested that binding of cholesterol in the cleft affects function by changing the conformation of helix II [41]. Molecular dynamics simulations have also suggested specific binding sites for cholesterol on rhodopsin [42] and a bound cholesterol molecule has been resolved in an electron crystallographic study of the metarhodopsin I intermediate of rhodopsin, bound at a site between two rhodopsin monomers [43]. Finally, a bound cholesterol molecule has been resolved in the structure of the (Na^+-K^+)-ATPase whose function is strongly dependent on the presence of cholesterol [44].

Concluding remarks and future perspectives

This review started by drawing a convenient though doubtless oversimplified distinction between lipid-based and protein-based approaches to understanding lipid–protein interactions in biological membranes. Until fairly recently, the lack of molecular structures for integral membrane proteins meant that only a lipid-based approach was possible, but this has now changed. Not only do we now have crystal structures for a representative range of membrane proteins but many of the structures contain resolved lipid molecules. Some of these lipid molecules are deeply buried within the structure, such as the molecule of phosphatidylglycerol found in nitrate reductase A and shown in Figure 5a. In such cases, it is clear that the interactions between the bound lipid molecule and the protein can only be understood in molecular terms, in the same way that binding of any ligand to a protein is understood.

Showing less specificity are clefts between transmembrane α-helices, exposed to the lipid bilayer, where a variety of hydrophobic molecules including phospholipids (Figure 5b), cholesterol (Figure 6b) and other hydrophobic molecules (Figure 6a) can bind. The functional importance of lipid binding in such clefts is not yet clear. The flexibility of lipid fatty acyl chains makes them efficient solvators of the rough transmembrane surface of a membrane protein, and able to penetrate into cavities of various shapes and sizes on the protein surface [45]. To some extent therefore, occupation of clefts by lipid molecules is simply a manifestation of efficient solvation of the transmembrane surface.

The lowest level of structural specificity is likely to be shown by the annular lipid molecules binding to the transmembrane surface of an intrinsic membrane protein, although even here the presence of any clusters of positively charged residues (Figure 4) will result in some structural specificity. One can ask to what extent interaction with these surrounding annular lipid molecules shapes a membrane protein. The observation that membrane protein crystal structures determined in detergent micelles are, with very few exceptions, clearly appropriate models for the structures adopted in the native biological membrane, suggests that the extent of any such shaping will be minor. For example, the structures adopted by rhomboid protease crystallized from detergent and from lipid bicelles are almost identical, except for one flexible loop [35]. It seems that the gross structure adopted by a membrane protein in the absence of lipid, determined by the packing preferences of its transmembrane α-helices, matches the structure of the lipid bilayer adopted by the membrane lipids in the absence of a membrane protein, so that the membrane protein and the native lipid bilayer can come together with little distortion of either. Of course, by the process of reconstitution, we can insert a membrane protein into a bilayer with properties, such as hydrophobic thickness, that are very different from those encountered in the native membrane, and then the membrane protein and the lipid bilayer will not match, leading to distortion of the membrane protein and the changes of function that are often observed [16].

Even though the gross structure of a membrane protein is probably determined by the packing preferences of the protein itself, the chemical structures of the surrounding lipid molecules will have some effects on structure, particularly for amino acid residues located close to the membrane–water interface. Charge and hydrogen bond interactions between lipid molecules and protein residues at the membrane–water interface could be important. In particular, recent studies investigating the different effects of phosphatidylcholine and phosphatidylethanolamine on the function of membrane proteins have emphasised the importance of the ability of the lipid headgroup to participate in hydrogen bonding with a membrane protein rather than differences in material properties such as the tendency to form non-planar structures [19–21].

A full understanding of how a membrane protein functions within a membrane will require information on how all the lipid molecules surrounding the protein interact with it. Given the large number of lipid molecules interacting with a typical membrane protein, and given that each conformational state of a membrane protein could interact differently with its surrounding lipid molecules, achieving such a complete description is still a long way off: it will probably only be achieved by molecular dynamics simulations of the type described earlier in this review [34,41,42].

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