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Review

The membrane structure and function affected by water

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ABSTRACT

Various experimental data reveal intriguing peculiarities in structural properties of biomimetic membranes. Interestingly, one of the common alterations that is observed at the membrane-water interface underlines the important role of membrane hydration properties. A plausible mechanism of action in the case of many membrane additives seems to be in shifting the water encroachment the way that bilayers absorb more or less water molecules - one of the smallest and often neglected biomolecule. The difference in water interactions with different lipids and cholesterol has been noted at the interface and up to the bilayer center, the ion depending interplay between lipid-water and ion-water hydrations has been shown, and the anaesthetic effect also appears to link tightly to hydration, to discuss but a few examples. Although a complete understanding of the physicochemical processes taking place in biomembranes is not established fully, the understanding of lipid bilayer structural changes as a result of different properties of environment outside and/or inside the membrane provides a foundation for better insights into the structure-function relationships that most certainly take place in complex biomembrane systems.

1. Biomimetic membranes

Biological membranes are one of the most proliferated structural units in living cells and organelles, where they form a natural hydrophobic barrier separating internal and external environments. Their functions however go beyond being simple permeability barriers accommodating proteins, which is corroborated also by their complexity. The peculiarities of these complex mesoscopic assemblies stem from the variety of thermodynamic properties that are characteristic to each component of the lipidome's huge size and diversity (van Meer et al., 2008). In general, biomembranes are central to biological processes including the transport of materials, cell defense, recognition, adhesion, and signaling. The former, in particular, is tied to the structure and dynamics of the membrane's lipid bilayer. For example, bacteria are known to adjust their lipid compositions upon exposure to toxic organic solvents, a scenario which presumably alters their surface charge density to minimize permeability to the toxin, while preserving bilayer integrity (Weber and de Bont, 1996).

The membrane structural properties are in many cases determined primarily by the chemical composition. Overall, the data are consistent with the notion that hydrocarbon chains dominate the bilayer's response to temperature changes, while lipid headgroups govern bilayer packing (Kučerka et al., 2015). The localization of water molecules and hydration properties within membranes depend on both the lipid head group type and the organization of hydrocarbon acyl chains (e.g., gel, liquid-crystalline phase). For diacylglycerophospholipids for example, a markedly smaller area per lipid distinguishes phosphatidylethanolamine (PE) from other membrane lipids despite sharing the same glycerol backbone (i.e., phosphatidylcholine PC, phosphatidylglycerol PG, and phosphatidylserine PS). The tight lateral packing of PE molecules in the bilayer then points to the strong hydrogen bonding between these headgroups which in turn results in significantly reduced hydration. For example, the hydration of dilauroylphosphatidylethanolamine (DLPE) in the Lα phase represents about 9 molecules of water per lipid (McIntosh and Simon, 1986), while a PC molecule in Lα phase imbibe about 25 waters, with about 10 of them located in the lipid head group region and the remains located in the fluid space between adjacent bilayers. Charged lipids, such as phosphatidylinositol (PI) or PS on the other hand, imbibe water without limits (McIntosh and Magid, 1993).

Cholesterol was found another modulator of lateral membrane organization in mammalian cell membranes (Silvius, 2003). The addition of cholesterol to fluid phase lipid bilayers results in increased acyl chain order (Chong and Cossins, 1984) while it decreases the extent of water penetration into the membrane's hydrophobic region. The opposite effect it has on lipid headgroups whose concomitant hydration increases with content of cholesterol. In turn, lipid headgroups are more

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separated and interactions between them are reduced. Thus, cholesterol appears also as a modulator of hydration. Although it is not completely clear how the cell manages a membrane's lateral organization, the segregation induced by cholesterol is supposed to be one of the key factors in formation of nanodomains (Simons and Ikonen, 1997). The hydrophilic and hydrophobic interactions are most likely one of the factors in the process. Consequently, the preferred interactions between its various components allow membrane to control their relative orientations and locations (Kučerka et al., 2009). In fact, it is even possible to imagine this mechanism resulting in the formation of functionalised nanodomains that facilitate a transport of biomolecules such as cholesterol, ions, and water. It should be pointed out that such wholesale movement across the bilayer may in turn control membrane protein function (Papanikolaou et al., 2005).

The specific functions occurring in the membranes can be plausibly correlated with the peculiar properties of their various components. In addition to the main building blocks of lipids and proteins, membrane components comprise many other additives of smaller or larger size that interact with membranes and in turn affect the structure and function of the biomembrane complex. The alkanes and primary alcohols are known to possess high biological activity and can act as general anesthetics (Forman and Chin, 2008). It is believed that such pharmacological effects are the results of their interactions with biomembrane components. One of the proposed mechanisms suggests that anesthetic effect stems from the structural changes to lipid bilayer induced by the interactions of general anesthetics with the membrane constituents (Haydon et al., 1977; Elliott et al., 1985). The structural changes observed in the case of alcohols suggest again the most important alteration at the membrane-water interface (Klacsová et al., 2011; Kondela et al., 2017). The water encroachment shifts the way that alcohol loaded bilayers absorb more water molecules when compared to the neat lipid bilayers, modifying commensurately the lateral pressure. This potentially affects the conformational space of membrane embedded ion channels and thus the wholesale function of membrane.

Besides proteins playing an active role in carrying out the various functions that take place in a biological membrane, its biological function is imparted also by much smaller additives. Intriguingly, we have noticed in our recent works a plausible correlation between the membrane structural changes and hydration properties of its various components. We review the results that support the case for water being one of the smallest biomolecules (Chaplin, 2006).

2. Membrane-ion interactions

Amongst the intramembrane interactions lipid-lipid, lipid-protein, and even protein-protein, the significance of ions for the proper functioning of biological membranes cannot be overestimated. They are ubiquitous in the cytosol and the extracellular fluid, and associate directly with plasma membrane properties such as membrane fluidity, bending and compressibility moduli, electrostatics, and aggregation and fusion. Their functions within cell membranes are understood to influence the gating of ion channels, membrane fusion, and membrane fluidity (Pabst et al., 2010). Although a complete understanding of these physicochemical processes has yet to be established, their functionality is known to depend strongly on the type of ion, the chemical composition of the membrane's interface, its thermodynamic state and a degree of hydration (Binder and Zschornig, 2002). Not surprisingly, Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+} or Cl^- have been found to play a prominent role also regarding the bilayer structure.

The primary effect of charged ions interacting with multilayered membranes is reflected in the increased lamellar repeat *D*-spacing that is the result of charge induced repulsion between the layers. The swelling in the presence of different types of salts has been reported for various zwitterionic lipid multilayers (Inoko et al., 1975; Petrache et al., 2006; Pabst et al., 2007; Alsop et al., 2016). It has been observed also in bacterial model membranes composed of smooth

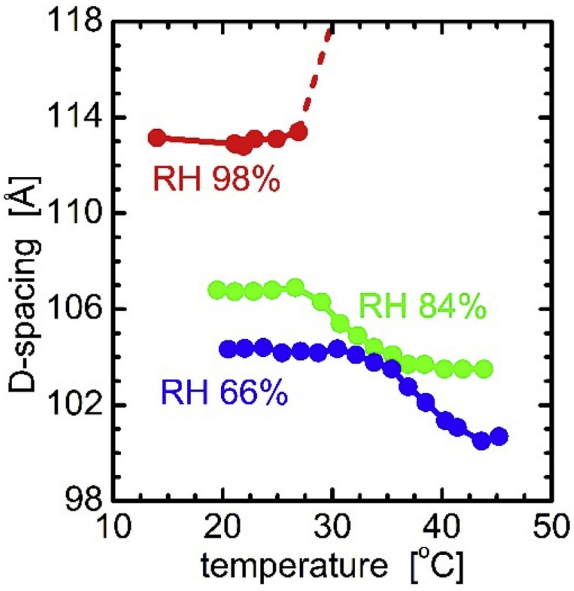

Fig. 1. Temperature dependence of the lamellar *D*-spacing obtained from neutron diffraction experiment at the various levels of relative humidity (RH) controlled externally. The multilamellar structure of Na^+-loaded LPS bilayers transitions from gel to liquid-crystalline phase at 66% and 84% RH. However, the interlamellar long range correlation disappears when temperature increases above 28 °C at 98% RH (adapted from (Abraham et al., 2007)).

lipopolysaccharides (LPS) (Abraham et al., 2007; Kučerka et al., 2008a). The data showed a significant amount of water penetrating even deep into Na^+ loaded LPS bilayers, including the bilayer's hydrophobic core centre. In fact, the disappearance of peaks in the neutron diffraction experiment when liquid-crystalline multilayers were subjected to high levels of hydration (see Fig. 1) suggested that the deep water penetration increases up to a critical point, beyond which the long range correlation of bilayer assembly is destroyed (Abraham et al., 2007). Such a destabilization may be a mechanism by which non-lamellar phases are formed and small molecules penetrate the outer membrane of Gram-negative bacteria.

The increased levels of hydration could be correlated with enhanced biological activities in biomimetic membranes which posts an intriguing research issue. The LPS membranes loaded with monovalent cations such as Na^+ have been reported measurably more active than those with some divalent cations, and orders of magnitude more active than with Ca^{2+} (Garidel et al., 2005). Commensurately, Ca^{2+} cations showed a restricted water penetration in the LPS bilayers, making them more compact and less permeable to water (Kučerka et al., 2008a).

The more detailed mechanism of the interaction of Ca^{2+} cation when compared to other divalent cations has been revealed effectively utilizing a model system (Uhríková et al., 2008; Kučerka et al., 2017). The results confirm that, Ca^{2+} and Zn^{2+} cations bind to dipalmitoylphosphatidylcholine (DPPC) bilayers as is reflected again in the increased lamellar *D*-spacing. In the case of vesicular systems in excess water condition, multilamellar DPPC dispersions convert completely into unilamellar vesicles when the surface charge density is higher than 1–2 μC/cm^2 (Hauser, 1993). More interestingly however, the low salt concentrations reveal the changes also to internal structure (see Fig. 2), while Ca^{2+} and Zn^{2+} do not have the same effects.

The Zn^{2+} impact shows a typical binding isotherm with a monotonic increase of bilayer thickness, after which it seems to plateau. A non-monotonic behaviour in the case of Ca^{2+}, however suggests inherent differences in the interactions of the two cations with lipid bilayers. The radial distribution functions calculated from molecular dynamics (MD) simulations (Kučerka et al., 2017) show that Ca^{2+} forms a contact pair with any headgroup atom of lipid much more favourably

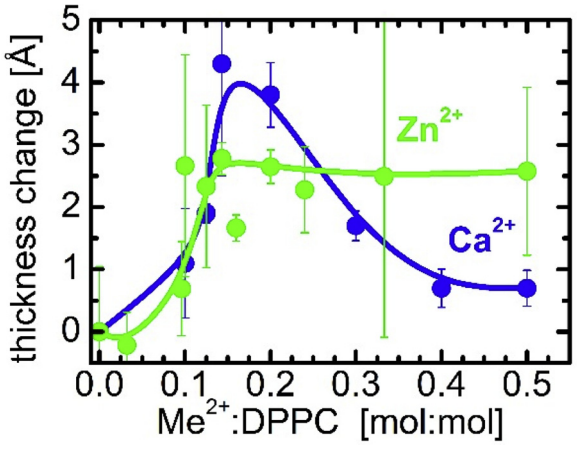

Fig. 2. Bilayer thickness changes with respect to neat DPPC bilayers as induced by divalent metal cations (Me^{2+}: Zn^{2+} or Ca^{2+}). The experimental data agree in the case of unilamellar vesicles dispersed in excess water (Uhríková et al., 2008, 2012) and in the case of slightly dehydrated planar multilayers (Kučerka et al., 2017), as obtained from neutron scattering and diffraction measurements, respectively.

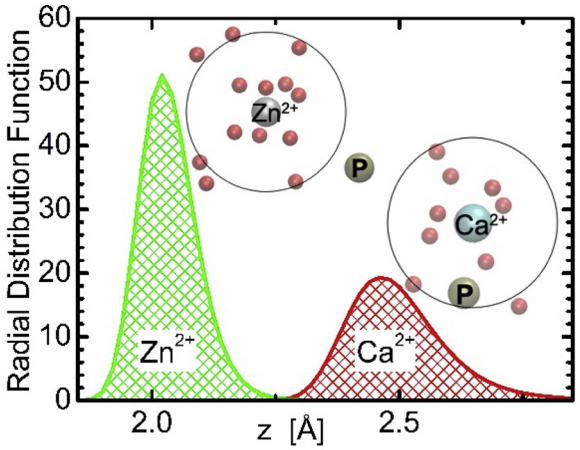

Fig. 3. Radial distribution functions for Zn^{2+} – and Ca^{2+} – water pairs determined from MD simulations (Kučerka et al., 2017). Areas under the peaks correspond to the number of water molecules present in the hydration shell of each cation. Corresponding hydration shells are sketched in the schematics suggesting fewer hydrating water molecules (red spheres) and closer proximity to the lipid's phosphate (P) in the case of Ca^{2+} cation.

than Zn^{2+}. These differences in the interaction specificity may be rationalized well by the hydration properties of the two cations. The hydrogen bonding of water molecules extends beyond the ion's primary hydration shell – their crystal arrangements in bulk water have been proposed to be $Zn[H_2O]_6^{2+}\cdot[H_2O]_{12}$ and Ca $[H_2O]_{6.1}^{2+}\cdot[H_2O]_{5.29}$ (David et al., 2001; Bock et al., 2003). Fig. 3 confirms that Ca^{2+} ions create about 1.6 times fewer pairs with surrounding water molecules than do Zn^{2+} ions, when interacting with DPPC bilayers. This smaller Ca^{2+} hydration shell then most likely allows for more proximal and stronger contacts with the lipid headgroup (see Fig. 3).

Intriguingly, the above-mentioned interactions become increasingly important when functionalizing the model membrane systems with specific applications such as drug and/or gene delivery (Uhríková, 2014). The role of water molecules that moderate the interplay of such interactions between various components of biological membrane can thus be seen as a certain link between its structure and function.

3. Cholesterol in biomembranes

Cholesterol is an essential component of mammalian cells, where it is required for building and maintaining the stability and fluidity of membranes. Cholesterol has also been implicated in cell signaling processes, where it has been suggested that it triggers the formation of lipid rafts in the plasma membrane (Simons and Ikonen, 1997). It is the interaction of cholesterol with the fatty acids of phospholipids that is believed to play a crucial role in modulating molecular organization within membranes. Its interaction with saturated chains is well known to disrupt the regular packing of chains in the gel-like phases while it restricts the reorientation of lipid chains in the liquid-like phases (Vist and Davis, 1990). Within the saturated membrane thus the cholesterol's steroid moiety orients parallel to the lipid chains, while its hydroxyl group locates just below the aqueous interface. Cholesterol acts effectively as a spacer between lipid molecules, resulting in the more hydrated lipid headgroups (Kučerka et al., 2007; Gallová et al., 2011). Water-cholesterol and water-lipid interactions therefore become obviously important in the dynamical balance of forces within the membrane.

The stability of water-membrane interface is maintained through the hydrogen bonding established between membrane components such as lipids and cholesterols, and water molecules, wherein they all may act as a donor and an acceptor. The primary targets of water for the formation of hydrogen bonds within lipids are the non-ester phosphate oxygens and the carbonyl oxygens, and hydroxyl oxygens in the case of cholesterol (Pasenkiewicz-Gierula et al., 1997; Henin and Chipot, 2006). The alternate hydrogen bonded complexes of cholesterol, water, and lipid also occur, while forming clusters of two to seven molecules. Importantly, the hydrogen bond network is a dynamic structure with the frequent switching of bonding partners. An example of this process is shown in Fig. 4, where the hydrogen bonding partner of the cholesterol's hydroxyl switches from the lipid's phosphate to the carbonyl. In addition, the cholesterol's hydroxyl is accompanied by some water molecules that are hydrogen bonded to it during the entire process. One can speculate that the latter creates a locally polar environment, which stabilizes the cholesterol hydroxyl even within the nonpolar bilayer core (Kučerka et al., 2008b).

The lipid-cholesterol interactions are modulated by the membrane disorder, which increases with temperature and unsaturated lipid content, but decreases with lipid chain length (Marquardt et al., 2016). Thinner and more disordered lipid bilayers experience a larger degree of cholesterol interdigitation between the two bilayer leaflets because

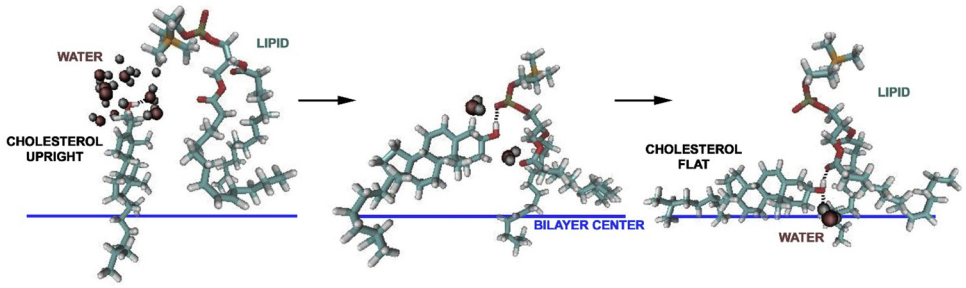

Fig. 4. The snapshots of MD simulations portraying the dynamics of hydrogen bonding that promotes a reorientation of cholesterol from its canonical upright orientation to the flat orientation (adapted from (Kučerka et al., 2008b)). Cholesterol's hydroxyl group establishes hydrogen bonds (broken lines) with water molecules and/or lipid headgroup. The accompanying water molecules may facilitate the reorientation of cholesterol when the atoms involved in hydrogen bridging come close to the bilayer center (blue line).

their hydroxyl's hydrogen bonding partners are closer to the bilayer center. Such disordered membranes are also significantly more permeable to water. These two features then can collaboratively result in a non-canonical orientation of cholesterol. With increasing membrane disorder, it is possible for cholesterol reorienting into the orientation perpendicular to the lipid chains, while it lies flat in the bilayer center as revealed by MD simulations results shown in Fig. 4 (Kučerka et al., 2008b).

Interestingly, the results of MD simulations have been observed also experimentally. Neutron scattering studies enabled to locate cholesterol in bilayers made of poly-unsaturated lipids. These bilayers characteristic of a very high disorder have revealed cholesterol preferentially sequestered near their center (Harroun et al., 2006, 2008; Kučerka et al., 2010). These results then provide further evidence on how different lipid species, their thermodynamic properties, and hydration conditions may affect the transversal, as well as the lateral organization in membranes. For example, the plasma membranes are known to be populated with more ordered components primarily in the outer monolayer (Brown and London, 2000), whereas more disordered components with the higher water permeability are more abundant in the inner leaflet (Knapp et al., 1994). The presence of a large and diverse group of lipids varying in their physico-chemical properties, hydration, and affinity to other membrane components, suggests the structural, and perhaps even functional, significance of lipid diversity exhibited by the lipidome.

4. Anesthetic effect

The capacity to interact with biological membrane and modulate its functionality defines the biological activity of a substance. In the case of long chain alcohols, such biological activity resulting in an anesthesia effect have been known to surgeons for over a century (Robinson and Toledo, 2012). Despite their successful applications however, the understanding of anaesthesia mechanism is still lacking. According to the general consensus, the place of their action is being recognised either within proteins or lipid membrane (Mullins, 1954; Lee, 1976; Franks and Lieb, 1982). However, the hypothesis based on the unspecific interactions between anesthetics and membrane lipids may be more plausible due to a wide spectrum of membrane proteins that are affected. In any of the two cases, the general anaesthetics offer an exciting example on the structure-function correlation that is sought out in biological membranes.

Amphiphilic molecules, like long chain alcohols, intercalate into membranes and change their structural and/or dynamical properties, which in turn might affect the membrane-bound protein conformations and result in protein functional changes. Both, the bilayer transversal structure and the dynamics of hydrated membrane system is reflected in the lamellar *D*-spacing that can be obtained straightforwardly from diffraction experiments. It consists of two components: the total thickness of bilayer and the thickness of water layer in-between the bilayers. The water layer comes in as a result of interbilayer interactions that are characteristic to a given lipid composition and thermodynamic state including the hydration conditions. The neutron diffraction experimental results suggest changes in some of these characteristics upon the addition of alcohols, as the water layer thickness increases. On the other hand, it depends very little on the chain length of the added alcohol, proposing the major changes happening to the bilayer thickness itself (Kondela et al., 2017).

The bilayer thickness of alcohol loaded system increases as a function of alcohol's chain length (Fig. 5). This can be related directly to the increasingly larger van der Waals interactions between the hydrocarbon chains of alcohols and lipids. The order within the hydrocarbon chain region increases with increasing chain length (Kučerka et al., 2011). It is therefore not surprising to see the very same behaviour in the case of other experimentally obtained thickness parameters. Namely, the distance between the opposite lipid headgroups also increases as a function of alcohol's chain length (Fig. 5). Interestingly however, the two thickness parameters behave differently when comparing the alcohol loaded systems to those made of neat lipids. While the addition of any and all investigated alcohols increases the head-to-head distance, the total bilayer thickness decreases upon the addition of an alcohol (Fig. 5). In this, it is important to realize that head-to-head distance represents the inherent lipid membrane structure, and bilayer thickness relates to the water-membrane interface.

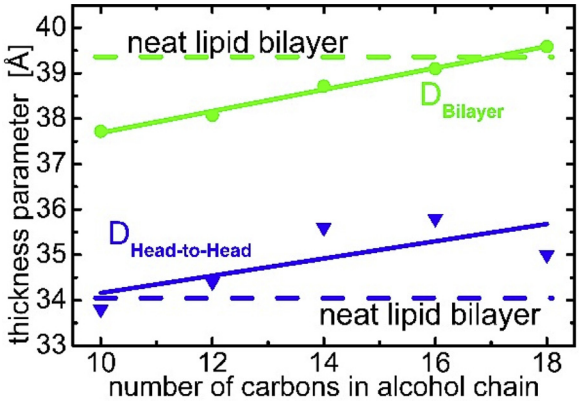

Fig. 5. The total bilayer thickness (green), and head-to-head distance (blue) obtained for neat lipid bilayers (dashed lines) and those with the addition of tail-length varied alcohols (solid points and solid lines). Neutron diffraction experimental results adapted from (Kondela et al., 2017).

The addition of alcohol to the lipid bilayer apparently produces changes in the lipid headgroup region, thus the water-membrane interface. The experimental results point directly to differences in the encroachment of water molecules (Kondela et al., 2017). The distance between the main headgroup position and water interface (distance between bilayer thickness and head-to-head distance) is fairly constant across the various alcohols discussed (3.7 +/-0.6 Å), while it is about 1.5 Å smaller than observed in the case of neat lipid bilayers. In other words, the addition of an alcohol results in some of the space in the polar headgroup region being filled with extra water molecules (Fig. 6).

The changes in water encroachment discussed above corresponds to less than 1 Å shift at each side of the bilayer. Even though it is a relatively small change, it is coupled to the increase in the lateral direction. The total increase of hydrating volume allows about one additional water per alcohol molecule to intercalate between lipid headgroups on each side. This in turn most likely impacts the membrane lateral pressure in the region directly above alcohols. The mechanism of anesthesia

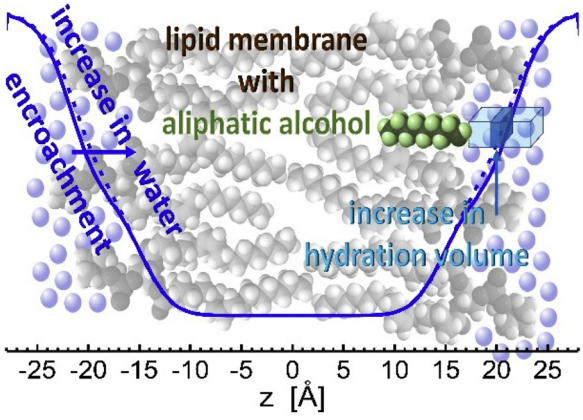

Fig. 6. Increase in water hydration at the water-membrane interface upon the addition of an aliphatic alcohol. Water molecules (blue spheres) fill an additional space (the dark portion of a blue rectangle) resulting from increased water penetration and enlarged lateral area above the alcohol molecule. Adapted from (Kondela et al., 2017).

effect then may be plausibly explained by the modulation of membrane mechanical properties by general anesthetics. Most importantly, such mechanism is related obviously to the hydration conditions of the membrane.

5. Conclusions

The proper functioning of biological membranes appears to be well correlated to the structural properties, thermodynamic conditions, and composition of lipid matrices. The various additives are known to enable or inhibit these functions provided, for the most part, by membrane proteins. Intriguingly, the action of these additives can be linked conceivably to another component of complex membrane assemblies – water. It creates a stable yet dynamic network around the membranes and down to their surfaces, by which it dictates the actual structure of bilayered membrane. It imparts the interactions between membrane and omnipresent ions to fine-tune its structure and most likely the function. It intercalates between the lipid headgroups at the water-membrane interface, wherein it modifies the lateral pressure that in turn impacts the proper function of membrane embedded proteins. It also penetrates the membranes much deeper, including its hydrophobic core, changing thus locally their properties and enabling other components to locate deep within membranes. Water is obviously one of the most prevalent molecules in membrane systems, their inseparable component, and a modulator of their structural properties that are reflected in their proper biological functioning. By virtue of the roles it plays, water should be considered a biomolecule.

Acknowledgements

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