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REVIEW

Biophysical effects of electric fields on membrane water interfaces: a mini review

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Abstract Lipid–water interfaces are dielectric transition regions. Their local organizations are highly sophisticated. They are sensitive to electric field with dramatic consequences on the global membrane organization and function. The importance of using local values of parameters (e.g. dielectric constant) near water–solution interface due to hydration and different electrostatic effects is often neglected in the description of cellular functions. Structural changes in the lipid layer are induced by minute changes in the electric properties of the interface. They bring alterations in the structure and oligomerization of membrane proteins.

Introduction

The purpose of this short mini review is to point out the effects induced by external electric fields on the structure of the interfacial region of lipid assemblies. This appears to be a neglected aspect of cell biology. The complex dynamical organization of this part of membranes will be reported in a synthetic way. The effects of lateral field will be described in a second part. The third part will report on what has been observed when transversal fields are applied. The consequence of the structural alterations of the interface on the cohesion of membranes will appear as a general phenomenon. The problems of very weak, but repetitive, field will be mentioned as a conclusion.

The main conclusions are that the interphase region appears as a decisive component in membrane behaviour and associated cell functions. This has to be taken into account in a biophysical description of cell biology.

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Biophysical complexity of the lipid–water interface

The most primitive description of the membrane–water interface is to consider that it is a local discontinuity between water and a charged flat surface. This is what is used in the Gouy Chapman model. Structural investigations by the use of NMR spectroscopy and X ray crystallography showed that the interfacial region was more complex (see Israelachvilli et al. 1980). The dynamic organization depends on interactions between neighbouring headgroups. Rotational movements are present along the normal to the plane of the layer as well as oscillations of the polar group axis around an average position sharply tilted from this normal. This average position is under the control of the electric local interfacial charge. Phospholipids were selectively deuterated at both methylene segments of the choline moiety and at the cis double bond of acyl chains. Deuterium, phosphorus, and nitrogen-14 nuclear magnetic resonance (NMR) spectra were recorded for liquid–crystalline bilayers to give structural informations on the different parts of the lipid molecules. The consequences of a modification of charges in the interfacial region by adding amphiphiles can be monitored. Although the hydrocarbon region and the glycerol backbone were not significantly influenced, significant perturbations that changed the orientation of the phosphate segment in the phosphocholine headgroup were induced. Changes in the electric surface charge control the phospholipid headgroup orientation and conformation (Seelig et al. 1987). Increasing the positive surface charge moves the N+ end of the dipole P–N toward the water phase (Scherer and Seelig 1989).

An up-to-date review of the different membrane potentials can be found in (O'Shea 2004 and references within). Two terms are specific of the interfacial region: surface potential and dipole potential (Fig. 1).

Surface potentials are primitively described by the Gouy Chapman theory. Their description is based on the Boltzmann equation, which describes the attraction of counter ions to the charged membrane surface (assumed to be flat and homogeneous). Improved versions of the Gouy-Chapman model of electrostatic properties of lipid membranes including hydration effects, polar head size and ion-correlations enable better agreement with experimental data (O'Shea 2004).

From a functional point of view, electrostatic repulsion (or attraction) towards the bulk phase appear as the clearest effect of surface potentials, as they may lead to the accumulation of charged solutes at the membrane surface (local pH effect).

The membrane dipole potential has a more molecular origin. It is due to the dipole moments of polar groups from the lipidic components of the bilayer, but it seems likely that the water molecules in the transition region between the phases may also make a contribution (Brockmann 1994). The dipolar groups are thought to be oriented in a way such that the hydrophobic interior of the membrane is positive with respect to the external aqueous phases and has a magnitude of several hundred millivolts (thought to be ca 300 mV).

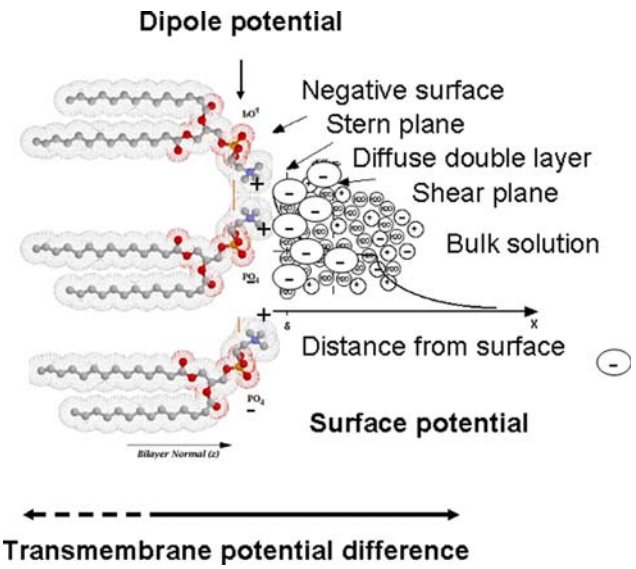

Fig. 1 Membrane potentials. The cartoon depicts the different partners of the lipid membrane–solution complex. Only half of a membrane is displayed. The bulk phase is on the left. Close to the lipid polar heads, an accumulation of negative charges is observed as well as a peculiar organization of the water molecules. This is the region where the position-dependent surface potential is present. The dipolar potential is associated with the polar heads. The polar headgroups are in a tilted orientation relative to the normal to the bilayer. The membrane potential difference is bulk to bulk

The magnitude of the dipole potential rises very steeply during passage from the water phase/membrane interface into the body of the membrane. The resulting forces on a polarized entity would decline just as steeply, however, as it moved more deeply into the body of the membrane. Therefore, by manipulating the dipole potential, it is possible to affect the extent of the penetration of peptides within membranes and therefore the resulting folding into secondary structures (Cladera and O'Shea 1998).

The contribution of water to the physical characterization of the interfacial region is sophisticated. A bioelectrochemical description (Teschke et al. 2001) gives the conclusion that interfacial water very close to the polar head is characterized by a very low electrical permitivity (Cherepanov et al. 2003). Electrostatic simulations give the conclusion that a potential barrier must be present 1 nm away from the surface membrane (assumed to be flat). The conclusion is therefore that a high proton concentration must be present in agreement with previous experimental observations on monolayers spread at the air–water interface (Prats et al. 1986). Water is an unusual substance playing a decisive role in the structure, dynamics and functions of membranes (Israelachvili 1992). Water molecules are dipoles. Endogeneous electric fields present in the interphase region induce a collective organization of interfacial water. The effect of an external electric field, i.e. a vectorial constraint, may bring a change in this collective organization. The local value of dielectric constant will be affected and as a consequence the local electrostatic forces.

A careful description of the local definition of the electrical constant is therefore needed in the interface. Using homogeneous values in "thick" layers is far from the biophysical behaviour of the interphase. Using this simplification gives an underestimation of the electrostatic forces that are present. This is a major setback as it is assumed that the electrostatic repulsive forces are a major contribution in the cohesive forces, assuming the cohesion of the membrane. Alterations in the electrostatic interactions among the phospholipid headgroups affect the local membrane curvature and the associated pressure stress (Fig. 2). This was shown to affect the oligomerization state of transmembrane proteins and their functions (Lundbaek et al. 1997). A decrease in the headgroup pressure due to the change in the electrostatic interaction will promote the binding of peripheral proteins and stabilize the oligomeric form of integral membrane proteins. This is predicted by calculations (Cantor 1999) and supported by the effect of non bilayer lipids (Van den Brink-Van der Laan et al. 2004).

Lateral field effects

The electrophoretic drag (motion of a particle in an electric field) is the most known effect. It was indeed used as

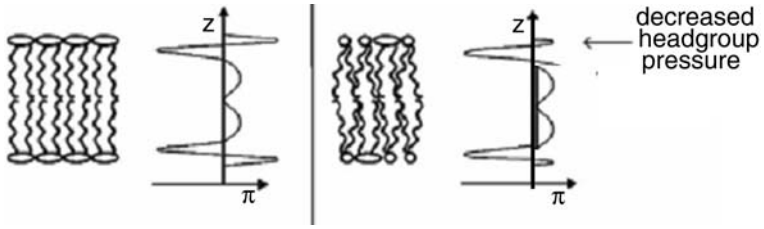

Fig. 2 Consequences of a change in the orientation of the polar headgroups. The figure on the left shows the initial configuration with a balance between the contributions of the different lateral surface pressure. The change in the orientation, which happens on the right results in a decrease in the repulsion at the level of the interphase. Less order is therefore present not only in the interfacial region, but with some consequences on the fatty acid chain region

one of the very first experimental evidences that a membrane can be assimilated to a fluid assembly where the different molecules can move when submitted to physical constraint (Poo and Robinson 1977). Nevertheless, electro-osmotic movements (due to the induction of flow at a charged surface by an electric field, the opposite of electrophoresis) must be taken into account, as a membrane interface can be considered as a charged wall if the surface charges can move only very slowly. The electrophoretic movement in the bulk phase induces a flow of liquid in the double layer very close to the interface. The induced hydrodynamic force draws the negatively charged membrane proteins in the opposite direction to that expected from electrophoresis.

But more complex processes can be induced in the lateral membrane organization when submitted to lateral electric field. The early report by McConnell and Lee was from experiments on lipid monolayers at the air–water interface. They observed that externally applied electric field gradients gave rise to lateral concentration gradients in monolayers of certain binary lipid mixtures. The lipid concentration gradients can be described by equilibrium thermodynamic chemical potentials. The observed effects appear to be relevant to the structure and composition of biological membranes (Lee et al. 1994; Lee and McConnell 1995). Under such conditions, nonuniform applied fields can produce or suppress phase separations with biological membranes that, at the growth temperature, are in a liquid state close to a phase boundary.

The geometries of lipid domains are under the control of a competition between line tension at the boundaries and dipole–dipole electrostatic repulsion between molecules in the different domains. In the case of lipids, the dipoles are associated with the polar head regions. An electric field gradient as was used in these studies will separate the phases with different dipole densities. Interactions between cholesterol and some phospholipids have been proposed to lead to the formation of condensed complexes. They appear to be sensitive to the lateral field gradient, which can destabilize these complexes, resulting in their dissociation (Radhakrishnan and McConnell 2000).

These observations on the primitive monolayer model were confirmed by studies using planar supported bilayers. Again, phase demixing was observed (Groves and Boxer 1995; Groves et al. 1998).

The lateral field can electrically control the spatial distribution of membrane–GPI linked proteins and give the formation of highly concentrated corals (Groves et al. 1996).

Such a sensitivity of the membrane organization and of domain formation implies that local electric fields play a very significant role in biological processes by acting on the dipole–dipole interactions. Interestingly, this may be used for biotechnological applications for the creation of specific domains or by using the concentrated corals for the bidimensional crystallization of GPI-linked proteins (Zasadzinski 1996).

Another conclusion is that critical demixing can be observed with a heterogeneous electric field of low magnitude, but the local distribution of the membrane components is altered over the course of a few microseconds (Groves et al. 2000).

This effect may provide an electrostatic mechanism for the sorting of proteins into specific membrane microdomains. This model experimentally observed on model systems may be correlated with processes occurring in the membranes of living cells.

Transversal field effect

Membranes present permeability barriers to the movement of charged species. The transport of net charges across the leaky insulator offered by the membrane results in a bulk to bulk electrical potential difference across the membrane with a magnitude that is described by the Nernst equation (so called resting potential) (O'Shea 2004). As a result, a strong transverse electric field is present on the biological membrane. Fluctuations in the membrane potential differences result in fluctuations in the electric field.

This is well known to result in changes in the dynamic conformation of voltage-gated proteins (Posson et al. 2005). A more dramatic effect was the observation that the

insulator property of a membrane is transiently lost when an overcritical potential difference is present, as first reported in 1972 (Neumann and Rosenheck 1972). This critical state was obtained by an external field-driven redistribution of mobile ions at the membrane–solution boundary, bringing a transient change in the membrane potential difference (Maxwell Wagner polarization). This is classically observed in the electropermeabilization (electroporation) process (Robello and Gliozzi 1989). Indeed, little is known of the molecular mechanisms supporting this dramatic reorganization of the membrane. Possible mechanisms were proposed: formation of either structural changes due to electromechanical stress or formation of aqueous pores in the lipid part of the cell membrane, which decrease the free energy of the membrane–local phase transitions. The asymmetric behaviour of the membrane when submitted to the transversal electric field (Tekle et al. 2001) led to the hypothesis that a dramatic reorientation of the dipoles in the interfacial region was a decisive step (Schmeer et al. 2004) (Fig. 3).

It was mentioned in the first part of this mini review that polar head region organization was highly sensitive to the surface charge, with polar headgroups being considered as interfacial electrometers. NMR investigations of the lipid multilayers, where a transverse electric field was applied, were used to investigate the lipid organization. It was concluded that the conformation of the headgroup was greatly affected, while no influence on the structure and dynamics of the hydrocarbon chains could be detected. A tilted orientation was induced by the field (Stulen 1981;Osman and Cornell 1994). This was predicted by Monte-Carlo simulations based on numerical modelling (Kotulska et al. 2007) and was interpreted as pre-pore structural changes, i.e. the induction step in electropermeabilization. Polarized attenuated total reflection (ATR) and Fourier-transform infrared (FTIR) spectroscopy were used to study the effect of electric fields on membrane molecule structure and orientation. This approach confirms fully reversible orientational changes in the lipid headgroups specifically induced by the electric potential difference (Le Saux et al. 2001; Bin et al. 2005a, b, 2006; Garcia-Araez et al. 2006; Zawisza et al. 2007). This approach brought more structural details on the field effect. On one side, the field drives the polar groups into the hydrocarbon layer, exerting a pressure and penetrating them, while on the other side, an erected configuration is induced (Fig. 3) (Miller 2002).

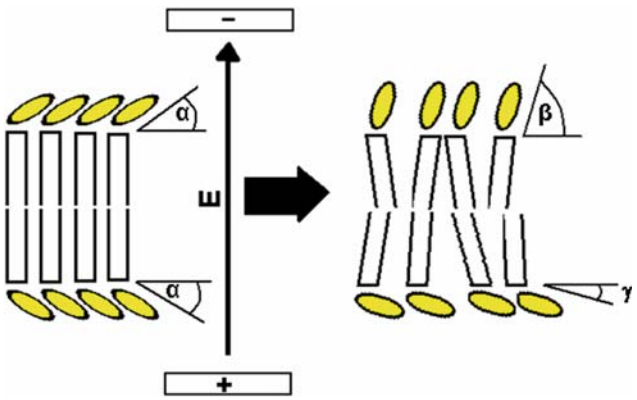

Fig. 3 Effect of a transverse field on the headgroup configuration. On the left, a symmetrical orientation is observed on the two sides of the lipid bilayer. When the field is applied, on one side, the polar head groups are pushed towards the membrane, while they are brought to an erected configuration on the other

As a result of this change in the organization of the polar head region, the thickness of the lipid bilayer is affected. The tilt orientation of the fatty acid chains was affected, as observed by neutron reflection and FTIR spectroscopy (Schwarzott et al. 2004; Burgess et al. 2004, 2005).

While the magnitude of the observed effects may be to some degree sample dependent (monolayers spread at the air–solution interface, planar bilayers supported at conductive and nonconductive surfaces, unilamellar vesicles, stacks of multiple bilayers), they all pointed out to a field-dependent structural change of lipid assemblies. The dramatic structural changes appear as a result either of the electrostatic pressure or more probably of the change in the balance of forces acting on the cohesion of the membrane.

These structural reorganizations should be taken into account when the response of membrane proteins to transmembrane voltage modulation are analysed. The change in the orientation of the interfacial dipoles results in an alteration of the local interfacial lateral repulsion and pressure on proteins. This is prone to alter the association of oligomeric proteins. The associated changes in thickness will affect the hydrophobic mismatch.

A more direct effect on intrinsic proteins of the transmembrane electric field is indeed present. It is well known that the activity of an ion pump is under the control of the transmembrane potential difference. A molecular description of the events affecting the protein conformation when a time-dependent electric modulation was applied led the "electroconformational" hypothesis to support the experimental observations (Tsong 1992) Again the vectorial character of the mechanism related to the transversal field effect on membrane must be taken into account to explain the potential effects of a random external field (Xie et al. 1994). This vectorial property may explain the sensitivity of biological systems to very weak oscillating external fields, where a response can be obtained below the thermal noise limit (Weaver and Astumian 1990; Astumian et al. 1995). A cumulative effect of the field effect would be present along the train of pulses.

Conclusions

The main target of this mini review is to convince the reader that a membrane is not limited in cell biology to a barrier function (the "bag" containing all the interesting and active molecules). The different "membranes potentials" (O'Shea 2004) are indicators and motors of the cell state. They are clearly affected by local external (and endogeneous) fields. The dipolar character of the interphase region makes it a target of these effects. The resulting structural and plurimolecular organization alterations are effective contributions to the membrane organization, dynamics and functions.

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