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ORIGINAL ARTICLE

Membrane–drug interactions studied using model membrane systems

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Abstract The direct interaction of drugs with the cell membrane is often neglected when drug effects are studied. Systematic investigations are hindered by the complexity of the natural membrane and model membrane systems can offer a useful alternative. Here some examples are reviewed of how model membrane architectures including vesicles, Langmuir monolayers and solid supported membranes can be used to investigate the effects of drug molecules on the membrane structure, and how these interactions can translate into effects on embedded membrane proteins.

1. Introduction

The majority of drugs are designed to target membrane proteins, since most diseases are related to the malfunction of these proteins (Yildirim et al., 2007). For example, drugs have been designed to block channel activities or inhibit protein binding (Cohen, 2002). Whilst drug–protein interactions have been systematically studied, the interactions of drugs with the membrane surrounding the proteins are often neglected. Membrane proteins require an adequate membrane as a surrounding support to ensure their structural and functional integrity. The natural membrane is a complex system, composed of a wide variety of different constituents such as lipids, carbohydrates and proteins. The exact membrane composition varies from organism to organism, even though there are some common characteristics for membranes from similar organisms (Escriba et al., 2008; Dowhan, 1997).

Membrane proteins themselves are in most cases rather fragile and unstable and typically denature once extracted from a membrane. Therefore, to fully understand the functional properties of a membrane protein, it has to be studied being embedded in a lipid bilayer membrane. The natural cell membrane, however, is a very complex and highly diverse system, comprising a large variety of different lipids, sterols and carbohydrates, yet the composition of the membrane and its structure play an important role in the functioning of the embedded membrane proteins. For example, changes in the membrane curvature can lead to an opening or closing of mechanosensitive membrane channels (Perozo et al., 2002).

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Despite the importance of the membrane, the influence of drugs on its structure and function is often neglected in drug related studies. Similarly, how drug-induced changes of the membrane properties influence the function of embedded membrane proteins is rarely investigated. This is partially due to the high complexity of the membrane, which renders systematic investigations very challenging. Additionally, experiments using whole cells or natural cell membrane patches are often time- and cost-intensive and mostly not suitable for routine screening. Finally, non-specific drug–membrane interactions, where the drug binds to the membrane, effectively reduce the available free drug, and thus make the treatment potentially less efficient (McLure et al., 2000; Nagar and Korzekwa, 2012; Smith et al., 2010). Thus it is clear that probing the membrane role in drug interactions is critical to a complete understanding.

Biomimetic model membrane systems offer an alternative platform to the natural membrane and enable the study of membrane–drug interactions under very defined and controlled conditions. The underlying structure of any membrane is a lipid bilayer. Different model systems have been developed to mimic the fundamental structural and functional properties of this bilayer. Very prominent examples for model membrane systems are vesicles or liposomes, Langmuir monolayers, solid supported bilayers and tethered bilayer lipid membranes. All of these systems offer certain advantages and disadvantages for the study of drug–membrane interactions. However, all of these architectures have been extensively characterised and analysed using a variety of biophysical techniques. The intrinsic properties of these model systems are well studied. No model system will mimic all properties of a natural membrane, however, it has been shown that specific characteristics of a membrane can be simulated very accurately using model systems. This offers the possibility for systematic investigation into membrane-related processes. At the same time it is important that the results obtained from model systems are correlated and validated with findings in natural systems.

Here, some model membrane systems will be introduced with the specific emphasis on their use in drug–membrane interaction studies (see Fig. 1).

2. Model membrane systems

Liposomes or vesicles are spherical phospholipid bilayers that can be formed by extrusion of an aqueous lipid dispersion through a membrane with pores of defined size or by sonication of lipid dispersion. Liposomes can be relatively easily prepared as unilamellar or multilamellar structures. The composition of the bilayer can be varied including a wide variety of different lipids and other membrane components (Peetla et al., 2009; Chan and Boxer, 2007; Olson et al., 1979).

Whilst vesicles are easily accessible, the number of techniques that can be used limits studies using vesicles. In principle, two different types of experiments can be performed. Changes in the shape and size of the vesicles due to an external stimulus, e.g. the interaction with a drug, can be monitored using scattering techniques, such as light scattering, small angle X-ray or neutron scattering. These experiments, however, do not give any insight into changes in the functionality of the membrane. Functional properties of the membrane such as the transport of molecules across the bilayer using vesicles can be done by fluorescence studies (Domenech et al., 2009). In such an experiment, a liposome is typically loaded with a fluorescent dye and for example pore formation in the bilayer would lead to the efflux of the dye and thus a change in the measured fluorescence.

Multilamellar vesicles were used to investigate the interaction of the antibacterial compound Rifabutin with membranes of various compositions (Pinheiro et al., 2013). Typically, bacterial membranes contain a higher amount of phosphatidylglycerol headgroups, whereas mammalian cell membranes are dominated by phosphatidylcholine and phosphatidylethanolamine headgroups. In model systems, bacterial membranes are thus often mimicked by using for examples dipalmitoylphosphatidylglycerol (DPPG) lipids, whilst mammalian membranes are represented by dipalmitoylphosphatidylcholine (DPPC).

Rifabutin is a wide spectrum antibiotic, which has an intracellular target and thus has to cross the membrane in order to be active. Analysis of structural changes in the membrane induced by the presence of the drug can lead to indications about the mechanism of action. Small and wide angle X-ray diffraction techniques (SAXS and WAXS) were employed by Pinheiro et al. to show a preferential interaction of Rifabutin with membranes in the gel phase of a mammalian model system, which explains the non-toxic effect of the drug. In contrast, the drug induced pronounced structural changes in a bacterial model system even though the membrane was in a fluid phase, in good agreement with *in vivo* results (Pinheiro et al., 2013).

In another example of the use of liposomes, the effect of oritavancin, an antibiotic on membrane permeability and lipid

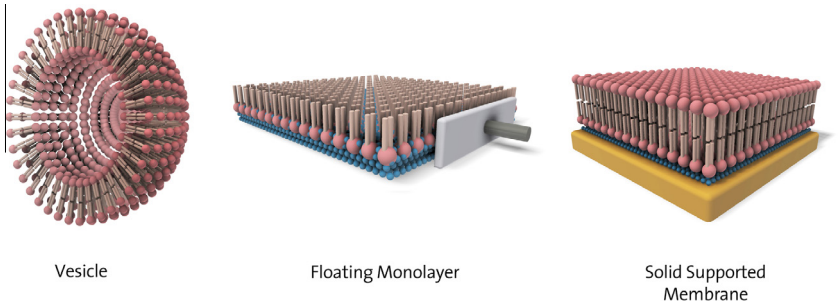

Figure 1 Schematic of different model membrane architectures: Vesicles, Langmuir monolayer and solid supported membranes. Vesicles are spherical assemblies of lipids (headgroups shown as balls, tails as sticks). Floating or Langmuir monolayers are assemblies of lipids at the air/water (blue balls) interface, whilst solid supported membranes are lipids bilayers at a solid support, often separated by a thin water layer.