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Review

Shedding light on the puzzle of drug-membrane interactions: Experimental techniques and molecular dynamics simulations

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ABSTRACT

Lipid membranes work as barriers, which leads to inevitable drug-membrane interactions in vivo. These interactions affect the pharmacokinetic properties of drugs, such as their diffusion, transport, distribution, and accumulation inside the membrane. Furthermore, these interactions also affect their pharmacodynamic properties with respect to both therapeutic and toxic effects. Experimental membrane models have been used to perform in vitro assessment of the effects of drugs on the biophysical properties of membranes by employing different experimental techniques. In in silico studies, molecular dynamics simulations have been used to provide new insights at an atomistic level, which enables the study of properties that are difficult or even impossible to measure experimentally. Each model and technique has its advantages and disadvantages. Hence, combining different models and techniques is necessary for a more reliable study. In this review, the theoretical backgrounds of these (in vitro and in silico) approaches are presented, followed by a discussion of the pharmacokinetic and pharmacodynamic properties of drugs that are related to their interactions with membranes. All approaches are discussed in parallel to present for a better connection between experimental and simulation studies. Finally, an overview of the molecular dynamics simulation studies used for drug-membrane interactions is provided.

Contents

Abbreviations: Chol, cholesterol; DAPC, 1,2-diarachidoyl-*sn*-glycero-3-phosphocholine; DLPC, 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine; DMPC, 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine; DOPC, 1,2-dioleoyl-*sn*-glycero-3-phosphocholine; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; DPPG, 1,2-dipalmitoyl-*sn*-glycero-3-phosphoglycerol; DPPS, 1,2-dipalmitoyl-*sn*-glycero-3-phospho-L-serine; DSC, differential scanning calorimetry; DSPC, 1,2-distearoyl-*sn*-glycero-3-phosphocholine; FDA, Food and Drug Administration; ITC, isothermal titration calorimetry; MD, molecular dynamics; NSAID, nonsteroidal anti-inflammatory drugs; POPC, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine; POPG, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol; POPS, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phospho-L-serine; QSAR, quantitative structure–activity relationship; US, umbrella sampling; WHAM, weighted histogram analysis method.

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1. Introduction

Membranes are essential to life. They are responsible for preserving the homeostatic environment inside a cell and maintaining crucial cellular functions [1]. They are generally composed of phospholipids, proteins, and glycoproteins in varying proportions, according to the membrane type and their distinct and specific functions [1]. The membranes themselves are also involved in cell signalling, and they are significantly altered in the presence of environmental stimuli [2]. They work as a barrier, and both cell culture and in vivo studies have already shown that they strongly affect the pharmacokinetic properties of drugs, namely their diffusion, transport, distribution, and accumulation [3]. For instance, several resistance mechanisms of cancer cells are related to the alteration of the membrane biophysics through a change in their phospholipid composition, and consequently, their fluidity, order, lipid packing, and membrane potential [4]. A review of the properties of cancer cells, with respect to membrane biophysics and its impact on anticancer drug-membrane interactions, was recently published [5]. The well-known P-glycoprotein multidrug efflux pump is also a recognized resistance mechanism due to its key role as a hydrophobic vacuum cleaner [6]. Its function is highly related to drug-membrane interactions, as reported by several studies, which confirmed that this transporter selects drugs from the membrane rather than from the aqueous medium [6]. Therefore, lipophilic drugs, which easily penetrate cancer cell membranes, are also easily expelled by the P-glycoprotein [6]. Bacteria have also been reported to develop membrane-related strategies, such as changing their outer membrane composition and charge to modify their affinity to antibiotics [7,8]. Drug-membrane interactions are unavoidable since absorption and even therapeutic action depend on them. In fact, approximately half of the current commercial drugs target a membrane protein [1]. Additionally, drugs can also have intracellular targets or act directly on the membrane curvature or phase behaviour [9]. However, because a membrane is a consequence of a balanced environment, the topical action of a drug may result in the disturbance of its biophysical properties, including its integrity [2]. This can result in either therapeutic or toxic effects, depending on the target membrane.

To gain new insight into drug-membrane interactions, several biophysical techniques have been developed through the use of membrane models. Additionally, molecular dynamics (MD) simulations have been used to provide complementary information at the atomistic scale. Since no data of drug-membrane interactions are used in the method development, the simulations for these systems are predictive. Therefore, the main advantages of MD simulations are the capabilities to predict relevant properties and to obtain detailed atomistic information, where the latter is often not accessible by experimental methods. The disadvantage of simulations is their computational cost, which prohibits the possibility of performing screening studies with MD simulations. This might change in the future, as a recent example using MD methods in fragment-based drug design has demonstrated that MD might be possible for screening studies [10]. This review will provide a brief overview of the most common experimental techniques applied in the study of drug-membrane interactions. Furthermore, we will provide a theoretical background of MD simulations and their application in this field, particularly their usefulness in the determination of key pharmacokinetic properties, such as the partition and the location of a drug within a bilayer. Moreover, the use of MD simulations to study the effects of drugs on the biophysical properties of a membrane and on both therapeutic and toxic mechanisms will be discussed. Hence, by discussing MD methods and experimental techniques in parallel, the goal of this review is to better connect the two different approaches. In fact, the combination of experimental techniques and MD simulations has recently been used to investigate drug-membrane interactions (e.g., [11–13]). After introducing the theoretical background of the methods, we will provide details on the most important pharmacokinetic and pharmacodynamic properties. For these properties, we will discuss the corresponding experimental methods and the application of MD simulations to predict these properties. Additionally, we will provide an overview of MD studies that have investigated drug-membrane interactions, which are restricted to Food and Drug Administration (FDA) approved drugs.

2. Theoretical background

2.1. Membrane models and experimental techniques

Although the study of drug-cell membranes interactions is important, the complexity, heterogeneity and fragility of cells make it hard to successfully perform biophysical studies [3]. For instance, the influence of some variables, viz., pH, temperature and ionic strength, on cells is difficult to study since cell viability depends on a homeostatic environment. Furthermore, the study of specific bacterial membranes that belong to pathogenic strains requires access to particular facilities and is restricted by a number of security regulations. To overcome these difficulties, membrane model systems with a lipid organization that is similar to those observed in natural cell membranes have been developed [3,9]. These models can be used to perform an in vitro assessment of the membrane's biophysical properties [3,9]. The most commonly used models are micelles, lipid monolayers, supported lipid bilayers and liposomes [3,9]. Liposomes can vary in size (small, large or giant), and they can be divided into unilamellar or multilamellar liposomes depending on the number of bilayers [14]. The selection of the model and size depends on the specific aim of the study and the properties to be investigated. For instance, the amount of a sample present in multilamellar systems can be an advantage compared to that in unilamellar systems for the application of some experimental techniques, such as solid-state nuclear magnetic resonance, differential scanning calorimetry and X-ray scattering analysis [14]. On the other hand, unilamellar vesicles are reported to have a curvature that is more similar to biological cells and, consequently, they have been extensively used to study drug-membrane interactions [9]. Similarly, micelles can be used to study the effect of drugs on the structural organization of lipids due to their hydrophilic surface and hydrophobic core [14]. However, properties, such as the lateral pressure, packing and topology of the surfaces, are difficult to measure in three-dimensional spherical models, such as micelles and liposomes [14]. Thus, lipid monolayers at the air-water interface are useful for studying these properties [14]. Additionally, it is easier to evaluate the effect of drugs on the