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Review

In silico pharmacology: Drug membrane partitioning and crossing

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ABSTRACT

Over the past decade, molecular dynamics (MD) simulations have become particularly powerful to rationalize drug insertion and partitioning in lipid bilayers. MD simulations efficiently support experimental evidences, with a comprehensive understanding of molecular interactions driving insertion and crossing. Prediction of drug partitioning is discussed with respect to drug families (anesthetics; β-blockers; non-steroidal anti-inflammatory drugs; antioxidants; antiviral drugs; antimicrobial peptides). To accurately evaluate passive permeation coefficients turned out to be a complex theoretical challenge; however the recent methodological developments based on biased MD simulations are particularly promising. Particular attention is paid to membrane composition (*e.g.*, presence of cholesterol), which influences drug partitioning and permeation. Recent studies concerning *in silico* models of membrane proteins involved in drug transport (influx and efflux) are also reported here. These studies have allowed gaining insight in drug efflux by, e.g., ABC transporters at an atomic resolution, explicitly accounting for the mandatory forces induced by the surrounded lipid bilayer. Large-scale conformational changes were thoroughly analyzed.

Contents

Acronyms: ABC, ATP-binding cassette; ADME, absorption, distribution, metabolism and excretion; AMP, antimicrobial peptide; CG, coarse-grained; COX, cyclooxygenase; CYP, cytochrome P450; DLiPC, dilinoeyl-phosphatidylcholine; DOPC, 1,2-dioleoyl-sn-glycero-3-phosphocholine; GA, general anesthetic; GlpT, glycerol-3-phosphate:phosphate transporter; GLUT1, glucose transporter; GST, glutathione S-transferase; IF, inward facing; LA, local anesthetic; LacY, lactose permease; MATE, multi-antimicrobial extrusion protein; MD, molecular dynamics; MFS, major facilitator superfamily; MM/PBSA, molecular mechanics/Poisson-Boltzmann surface area; MM/GBSA, molecular mechanics/generalized born surface area; Msba, bacterial ABC lipid flippase; NAT, N-acetyltransferases; NBD, nucleotide-binding domains; NSAID, non-steroidal anti-inflammatory drug; NSS, neurotransmitter:sodium symporter; OAT, organic anion transporter; OF, outward facing; PEPT, peptide transporter; PIP2, phosphatidylinositol 4,5-bisphosphate; PMF, potential of mean force; POPC, 1-palmitoyl,2-oleoyl-sn-glycero-3-phosphocholine; POPG, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol; QM/MM, quantum mechanics/molecular mechanics; SLC, solute carrier; SULT, sulfotransferase; TM, transmembrane helice; TMD, transmembrane domain; UGT, uridine 5′-diphospho-glucuronosyltransferase; XylE, xylose:H+ symporter.

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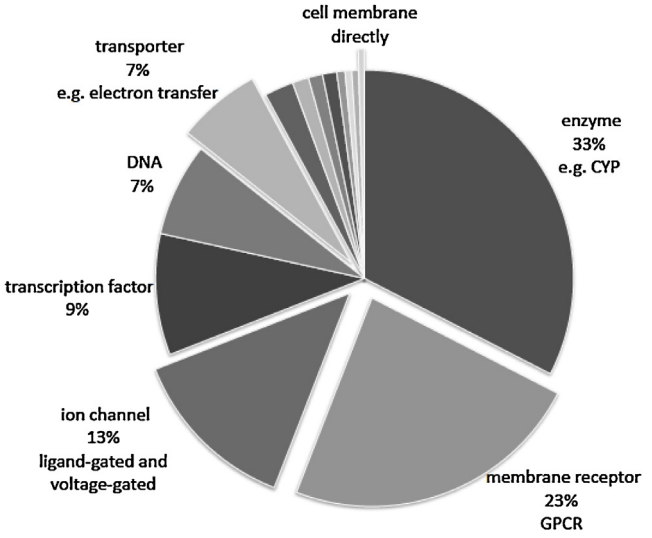
1. Introduction

Drug-membrane interaction is a crucial pharmacological step that directly affects ADME (absorption, distribution, metabolism and excretion) of drugs, and subsequently drug action or toxicity [1,2]. Biological membranes are complex dynamical systems composed of a huge number of different lipids and proteins, with mass ratio ranging from 1:3 to 3:1 [3]. According to the fluid mosaic model proposed by Singer and Nicholson in 1972, the plasma membrane forms "islands" of proteins immersed in the "two-dimensional sea" of lipids [4]. This model is still a valid description of most biological membranes with some significant exceptions, e.g., skin membrane [5].

In this review, we will mainly focus on drug interactions with the lipid bilayer and with membrane proteins. Although only about 30% of human genes encode for membrane proteins [6], more than 60% of molecular targets of commonly used drugs are membrane proteins (Scheme 1) [7]. Drug-protein interactions, related mechanism of a drug action, have been under close consideration [8], which is often better documented than drug-lipid interactions and membrane crossing. Drug-lipid interactions are pharmacologically significant as i) drug partitioning to membranes is more common than nonspecific protein binding [9]; ii) nonpolar xenobiotics can accumulate in lipid bilayers [10]; and passive transport contributes to drug disposition [11].



Scheme 1. 411 known targets of 1732 FDA approved drugs (up to 2015) according to ChEMBL21 dataset sorted by target type. Membrane bound targets consist about 62.4% are annotated by expansion of triangle.

The biophysical techniques used to investigate drug-membrane interactions provide meaningful but fragmented information on: drug insertion; average location in the inner or outer parts of lipid bilayers; conformational and orientational behaviors; diffusion coefficients; partition coefficients; and membrane (passive) permeation. The mentioned biophysical methods are rather expensive, time consuming and cannot be employed easily in high-throughput screening. Alternatively, *in silico* molecular modeling has gained substantial attention and maturity over the past decade. Since their conceptualization [12–14], the *in silico* membrane models have witnessed an extensive development [15–17]. The exponential growth of computing resources also drives the development in accuracy at reasonable time. Molecular dynamics (MD) simulations of lipid bilayer membranes evaluate drug-membrane interaction at both atomic and femtosecond resolutions, which is hardly reached simultaneously by experimental methods. This review will show how theoretical methods can now be considered as a new pharmacological tool, supporting or predicting experimental evidence, explicitly addressing: i) lipid bilayer insertion (Section 3); ii) passive membrane permeation (Section 4.1); iii) facilitated transport by membrane proteins (Section 4.2); iv) biotransformation by membrane proteins (Section 5); and v) efflux by active membrane transporters (Section 6).[1] Concerning the last three points, a particular attention will be paid to the role of lipid bilayers. The strengths of different *in silico* methodologies will be discussed, emphasizing on the importance of lipid bilayer composition (Section 7).

2. Glossary of *in silico* terms

The aim of this section is only to guide non-experts in the specialized vocabulary, so as to facilitate and focus on understanding of the physical-chemical picture of drug-membrane crossing.

2.1. Molecular mechanics

Methods to calculate the potential energy of a given molecular system as a function of position of the atoms in the system. The calculation is based on the classical (Newtonian) mechanics and empirical non-covalent terms as described by a force field.

[1] Active transport proteins require ATP-hydrolysis to function contrary to the facilitated transport, in which transporters use electrochemical gradient arising from the co-transport of smaller substrates (*e.g.*, H^+, Na^+).