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Computational studies of drugs in lipid membranes and liposomes

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Introduction

Lipid membranes play important roles in medical therapy as drug molecules are required to pass through the plasma membrane in order to reach molecular targets within a cell. Drug molecules can enter cells through passive diffusion and may reach their target cells encapsulated in carriers such as liposomes. Liposomes are artificial circular vehicles made from lipid membranes that can be used to effectively deliver drug molecules to specific tissues. The properties of the drugs determine how they interact with membranes and liposomes, and this subsequently determines their potential as therapeutic agents. Using computational methods we study how potential drug compounds interact with membranes and liposomes.

5-Aminolevulinic acid (5ALA) can be used as a pro-drug in photodynamic therapy (PDT), a method used to treat skin diseases and cancer using a photoactive agent that upon light excitation reacts with molecular oxygen and forms reactive oxygen species. 5ALA is via a number of enzymatic reactions endogenously converted into the photoactive compound protoporphyrin IX. We study 5ALA, its methyl ester (Me-5ALA) and four 5ALA oxime derivatives (HH, MH, HM, and MM) in dipalmitoylphosphatidylcholine (DPPC) lipid membranes.[1] The permeability of the drug molecules is calculated in order to determine their ability to enter a cell through diffusion.

Hypericin (Figure 1A) is a light-absorbing molecule naturally found in Saint John's wort (*Hypericum*) that may be used in PDT. The properties and permeability of hypericin and two brominated derivatives are studied in lipid membranes.[2,3] We study how various levels of cholesterol influence the permeability of the molecules in membranes. Hypericin is also studied in liposomes that are possible carriers of such hydrophobic molecules and their interactions with liposomes are investigated in detail.

Methods

Atomistic and coarse-grained molecular dynamics (MD) simulations were applied to study the behavior of the drug compounds in membranes and liposomes. In atomistic MD simulations atoms are treated either separately or non-polar hydrogens are combined into neighboring carbons (united-atom); the latter is a common method used to speed up simulations and this was applied in the membrane studies. The Gromos force field was applied throughout the membrane studies.

In coarse-graining several heavy atoms are grouped into coarse-grained particles in order to enable studies of large systems such as liposomes that contain thousands of lipids. The MARTINI force field was used in the coarse-graining study.[4] The coarse-grained models of hypericin and a DPPC lipid are displayed in Figure 1.

All MD simulations were performed in the GROMACS program.[5]

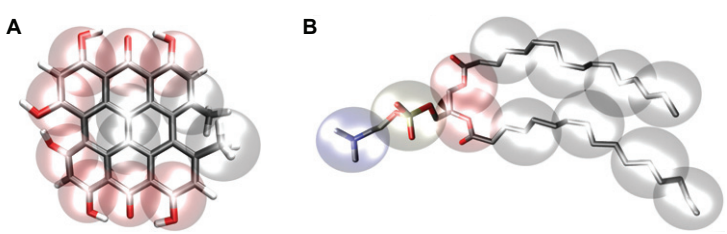

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Figure 1. Coarse-grained models of (A) hypericin and (B) a DPPC lipid. The large circles represent the coarse-grained particles.

Results and discussion

The 5ALA molecules diffuse into the lipids of the membrane where they accumulate during the MD simulations. Calculated permeability coefficients for diffusion of the 5ALA molecules through the membrane are displayed in Table 1. Me-5ALA exhibits more enhanced diffusion through the membrane compared to the other molecules, indicating that this molecule possesses suitable properties for translocating the plasma membrane and reach the interior of a cell, where it can be converted into protoporphyrin IX. Two of the oxime derivatives display enhanced properties compared to neutral 5ALA but none of the oxime derivatives could surpass Me-5ALA.

Table 1. Calculated permeability coefficients (P; cm/s) for 5ALA, Me-5ALA, and the 5ALA oxime derivatives inside a pure DPPC membrane

Molecule	*P*
5ALA	18.9
Me-5ALA	52.8
HH	29.3
MH	31.0
HM	4.9
MM	12.1

The hypericin molecules also accumulate in the lipids of the membrane, but closer to the interface between the lipids and water compared to the 5ALA molecules. A snapshot from a MD simulation of a membrane with hypericin is displayed in Figure 2A. Calculated permeability coefficients for the hypericin molecules in membranes with various concentrations of cholesterol are displayed in Table 2. The hypericin derivative with one bromine atom displays the easiest diffusion in all three membranes, with a permeability coefficient in the range of that for Me-5ALA. The permeability of the drug molecules is generally lower in the presence of cholesterol in the membranes due to its condensing and ordering effect.

Table 2. Calculated permeability coefficients (cm/s) for the hypericin derivatives inside DPPC membranes without and with cholesterol

Molecule	*0 mol% cholesterol*	*9 mol% cholesterol*	*25 mol% cholesterol*
Hy	4.2	8.2×10^{-8}	1.6×10^{-13}
Hy-Br	49.4	54.9	4.1
Hy-4Br	15.1	3.3×10^{-2}	6.9×10^{-7}

The hypericin molecules are highly hydrophobic and interact with each other in water. The molecules diffuse into the lipid region of the liposome during the MD simulations and accumulate in the same region of the lipids as in the membranes, however, only in the outer layer. A snapshot from a MD simulation of a liposome with hypericin is displayed in Figure 2B. Various numbers of hypericin molecules are included in order to predict the load capacity of the liposome.

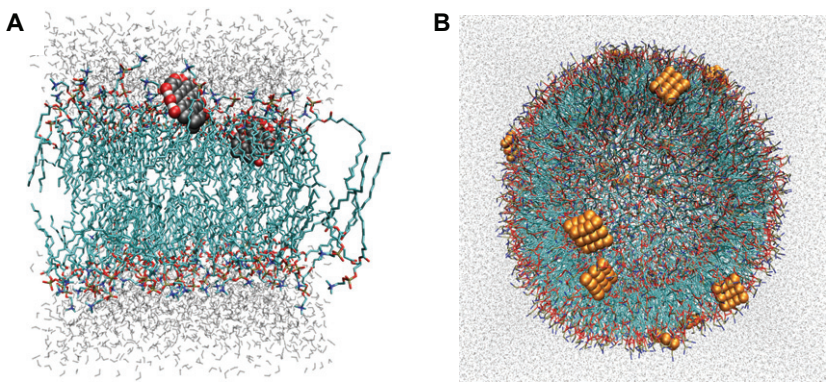

Figure 2. Hypericin molecules in (A) a lipid membrane and (B) a liposome. Hypericin is depicted as space-filling model in A, and as 'flat squares' in B.

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