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Studies on the interaction of α-cyclodextrin with phospholipid by a flexible docking algorithm

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Abstract

The single-molecule complexation model was provided to study the interactions of α-cyclodextrin with phospholipid components of the erythrocyte membrane using the flexible docking algorithm FDOCK. The energies and structures of the complexes between α-cyclodextrin and phospholipid at each different inclusion depth were calculated. In which, some important complexation states during the inclusion procedure were also investigated by molecular dynamics simulations. The results show that the phospholipid molecule cannot pass through the α-cyclodextrin cavity due to the prominent energy barrier when the two acyl chains are included into the α-cyclodextrin cavity simultaneously. The driving force responsible for the complexation of α-cyclodextrin with phospholipid is the van der Waals force. The complex structure of α-cyclodextrin with phospholipid acyl chain, comparing with that of headgroup, is of the lower energy. Furthermore, comparing with *sn*1 chain, the complex of *sn*2 chain with α-cyclodextrin is probably more stable due to the bendability of the unsaturated *sn*2 chain, which restricts α-cyclodextrin slipping on the acyl chain.

Keywords: α-cyclodextrin; Phospholipid; Flexible docking algorithm

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides formed by bacterial degradation of starch, and typically contain six, seven, or eight glucose residues linked by (1–4) glycosidic bonds [1]. They feature a relatively nonpolar cylindrical cavity, which can form complexes with the appropriate guest molecules [2,3]. As such, they have received increasing attention in the pharmaceutical field to modify the physicochemical properties of drug molecules, such as solubility, stability and bioavailability, reduce their toxicity and side effects, and suppress unpleasant taste or smell [4]. However, more interest is focused on the effectiveness of cyclodextrins in pharmaceutical applications, relatively little is known about the interactions of cyclodextrins and phospholipid components of the erythrocyte membrane. In fact, hemolytic character is also an important biomedical aspect of cyclodextrins. They can extract phospholipids from the erythrocytic membrane to form lipid-CD complexes [5]. Phospholipids are the major components of biological membranes and made up of a hydrophilic (polar) headgroup and a hydrophobic tail. This complex-mediated extraction of lipids from the membrane may increase the erythrocytic membrane permeability and result in the rupture of the erythrocytic membrane [5,6]. Experiments on the cyclodextrins inducing release of lipids from the cell membrane showed that phospholipids were the main target of α-CD [6], and the extraction ability of phospholipids from the membrane could depend on the nature of the polar headgroups of the phospholipids [7]. The interaction of α-CD with isolated phatidylinositol (PI) headgroup (i.e., without the acyl chains) was studied [8]. In order to investigate the complex of α-CD with each building block of the phospholipid molecule, the single-molecule interaction of α-CD with the complete phospholipid molecule was studied using the flexible docking algorithm FDOCK [9,10]. In this paper, the phospholipid molecule was moved from the narrow side of the α-CD cavity to the wide side along the *Z*-axis step by step to explore the possible binding regions of phospholipid in the cavity. Although it is a simplified model to the real membrane system, the results obtained are still valuable to understand the

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mechanism of α-cyclodextrin extracting the phospholipid from the membrane.

Our efforts in this paper have been devoted to investigating the energy of each complexation state and the complex structures of α-cyclodextrin with phospholipid during the inclusion procedure. The interactions of α-cyclodextrin with palmitoyloleoylphatidylinositol (POPI), especially some important complexation states, were investigated in detail by FDOCK. Furthermore, it was also validated by the results of studying several representative inclusion complexes using molecular dynamics simulations. The interactions of α-CD with palmitoyloleoylphatidylserine (POPS) and palmitoyloleoylphatidylethanolamine (POPE) were also studied using the same method and compared with that of POPI. By analyzing the energy distribution of each complexation state and the optimized complex structure, the driving force responsible for the complexation and the structural properties of the low-energy structure for each complexation state are very clear.

2. Theory and method

2.1. Molecular modeling

The initial structure of α-CD was taken from the crystal structure [11]. The original structure of POPE molecule came from Huang [12], in which, *sn*1 and *sn*2 chains are constituted of 16 and 18 carbons (numbered from the carbonyl group), respectively. A double bond exists between C_9 and C_{10} of *sn*2 chain. The structures of POPI and POPS were deduced from POPE by replacing the ethanolamine group by inositol group [13,14] and serine group, respectively. The structure scheme of the three phospholipids molecules was given in Fig. 1. All the initial structures were energy-minimized using the conjugate gradient method under the CFF91 force field in the Discover module of Insight II. In this study, the phospholipid molecule was moved toward and forced to penetrate the α-CD cavity step by step with the preferential orientation reported by Ref. [15], i.e., the phospholipid headgroup facing the narrow side of the α-CD cavity, and keeping the orientation during the moving. Considering POPI as an example, the scheme of phospholipid penetrating the α-CD cavity was shown in Fig. 2. In which, α-CD was oriented to have almost all the glycosidic oxygen atoms in the *XY* plane, and the origin of the coordinate system was placed at the geometry center of α-CD. The *Z*-axis is perpendicular to the *XY* plane through the origin and pointing to the primary side of α-CD. The position of the phospholipid molecule in the α-CD cavity is defined by the coordinate of its geometry center. Therefore, the *Z*-coordinate represents the geometry center position of the phospholipid molecule relative to α-CD, reflecting the inclusion depth of the phospholipid molecule in the cavity.

2.2. Flexible docking

In our initial study, the inclusion complexes of CD with the less flexible molecules, such as benzene derivatives, were investigated using a rigid docking method, and the results were in good agreement with the experimental results [16]. However, for the more flexible system, the conformational changes of the interactive molecules need to be taken into account. For that, we developed a flexible docking program FDOCK, in which six degrees of translational and rotational freedom of one molecule

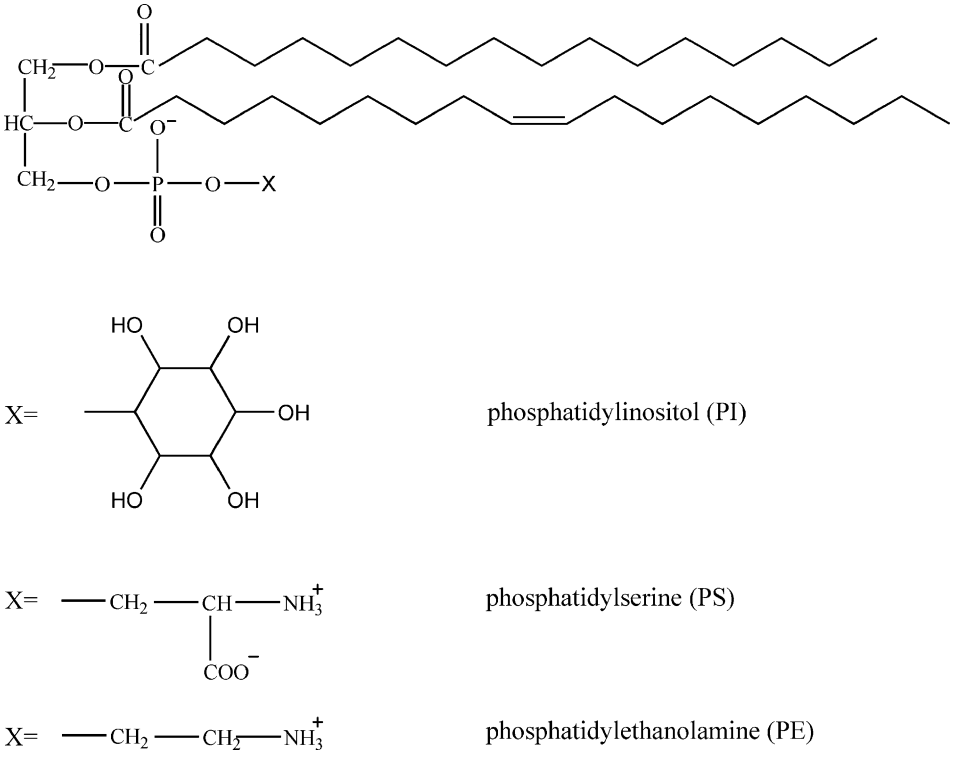

Fig. 1. The structure of three phospholipids.