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The biophysical properties of ethanolamine plasmalogens revealed by atomistic molecular dynamics simulations

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ABSTRACT

Given the importance of plasmalogens in cellular membranes and neurodegenerative diseases, a better understanding of how plasmalogens affect the lipid membrane properties is needed. Here we carried out molecular dynamics simulations to study a lipid membrane comprised of ethanolamine plasmalogens (PE–plasmalogens). We compared the results to the PE–diacyl counterpart and palmitoyl-oleyl-phosphatidylcholine (POPC) bilayers. Results show that PE–plasmalogens form more compressed, thicker, and rigid lipid bilayers in comparison with the PE–diacyl and POPC membranes. The results also point out that the vinyl–ether linkage increases the ordering of sn-1 chain substantially and the ordering of the sn-2 chain to a minor extent. Further, the vinyl–ether linkage changes the orientation of the lipid head group, but it does not cause changes in the head group and glycerol backbone tilt angles with respect to the bilayer normal. The vinyl–ether linkage also packs the proximal regions of the sn-1 and sn-2 chains more closely together which also decreases the distance between the rest of the sn-1 and sn-2 chains.

1. Introduction

Plasmalogens are a special subclass of glycerophospholipids that are characterized by the presence of a vinyl–ether linkage at the sn-1 position, and an ester linkage at the sn-2 position. Plasmalogens are found in nearly all animal and anaerobic bacterial cells [1], and they constitute 15–20 mol% of total phospholipids in the cell membranes [2,3]. Furthermore, plasmalogens are also found in subcellular membranes as well as in specialized membranes such as myelin and synaptic vesicles [3,4]. Interestingly, plasmalogen ethanolamines (PlsEtn) constitute up to 85 mol% of total phosphatidylethanolamine (PE) species and up to 30 mol% of total phospholipids in nerve tissue membranes [3].

The role of plasmalogens in cell membranes has aroused scientists' interest for decades since it has been found that the amount of plasmalogens is reduced in various neurodegenerative disorders, such as Zellweger syndrome (ZS), Alzheimer's disease (AD), and Down syndrome (DS) [3,5]. In the case of AD and DS the reason for the reduction of plasmalogens is poorly understood, but in the case of ZS a plasmalogen deficit is a direct consequence of the genetic defect.

For instance, patients suffering from Alzheimer's disease (AD) have been shown to have decreased levels of plasmalogens in brain areas that are under degeneration, and the extent of reduction correlates with the severity of the disease [3,6]. Because plasmalogens are important constituents of various lipid membrane structures and their central role in different human disorders, it is essential to determine their biophysical properties and what kind of changes these features exert on lipid membrane structure and dynamics, as well as on the function of membrane proteins. In this way, new information will be discovered leading to a comprehensive understanding of the processes mediated by plasmalogens.

Concerning the biophysical properties of plasmalogens, experiments have demonstrated that plasmalogens have lower lamellar gel to liquid-crystalline and lamellar to inverse-hexagonal phase transition temperatures compared to alky and diacyl counterparts [7–9]. Moreover, the plasmalogen-deficient cells derived from patients affected with the Zellweger syndrome (plasmalogen content 0–5% of total phospholipids) showed lower fluorescence anisotropies corresponding to higher membrane fluidity and decreased order compared to the controls (plasmalogen content 13–15%), suggesting that plasmalogens rigidify biological membranes [10]. Further, since ethanolamine plasmalogens have a stronger tendency to promote the formation of inverted hexagonal phases, they are suggested to facilitate membrane fusion events in different contexts [5]. However, the sub-molecular details behind the above properties are not fully understood, although NMR spectroscopy measurements have suggested that the vinyl–ether linkage at the sn-1 position induces a conformational change to the glycerol backbone driving the closer packing of the sn-1 and sn-2 chains at the proximal region

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[11]. This in turn induces a closer packing of lipids at the water–lipid interface, which may promote the formation of the inverted hexagonal phase by reducing the area taken by the lipid head group. Further, it was shown that the orientation of the polar head group with respect to the membrane surface differs between choline plasmalogens and diacyl phosphatidylcholine [12].

Aside from the importance of plasmalogens on the structural features of lipid membranes, they are important antioxidant agents and lipid mediators. Since the vinyl–ether bond is highly sensitive to oxidative attack compared to their ester counterparts, it has been suggested that plasmalogens act as molecular scavengers, protecting cells and especially lipids from oxidative damage [13]. Furthermore, as plasmalogens often contain arachidonic acid (AA) or docosahexaenoic acid (DHA) at the sn-2 position, they are important in the synthesis of eicosanoids and in the signal transduction processes via plasmalogen-selective-PLA2-mediated release of DHA and AA [14].

In the present study, our aim is to clarify the molecular properties of ethanolamine plasmalogens (PE–plasmalogen) and especially the role of vinyl–ether linkage utilizing atomistic molecular dynamics simulations. Thus, we simulated three bilayers systems comprised of either PE–plasmalogen PE–diacyl, or POPC lipid species. The results revealed that PE–plasmalogens lipids form more condensed and rigid bilayers compared to their diacyl counterparts and POPCs. These features were influenced by the vinyl–ether linkage due to its marked effects on the properties of the sn-1 and sn-2 chains.

2. Materials and methods

2.1. Simulated systems

In this study, three different lipid bilayer systems were studied: a PE–plasmalogen bilayer system (P-16:0/20:4), a PE–diacyl bilayer system (16:0/20:4) and a POPC bilayer system (16:0/18:1). According to the literature, PE(P-16:0/20:4) is not decreasing during AD [3]. However, it has been found that the reduction of PE(P-16:0/20:4) correlates with severity of AD related cognitive impairment although it does not correlate with post-mortem AD pathology [15]. The diacyl counterpart system was chosen in order to reveal the effect of the vinyl–ether linkage on the properties of plasmalogens. The POPC bilayer was chosen for comparison purposes because it is one of the most abundant lipid species in biological membranes and because it is experimentally as well as computationally well characterized. Each lipid bilayer system consisted of 128 lipid and 3500 water molecules. The chemical structures for the simulated lipid species are shown in Fig. 1.

2.2. Force field and simulation parameters

To parameterize lipid molecules, the OPLS-AA (Optimized Potentials for Liquid Simulations-All Atom) force field was used with recently derived parameters for the long hydrocarbons, glycerol backbone and head group (so-called MACROG lipids) [16]. For unsaturated lipids, a

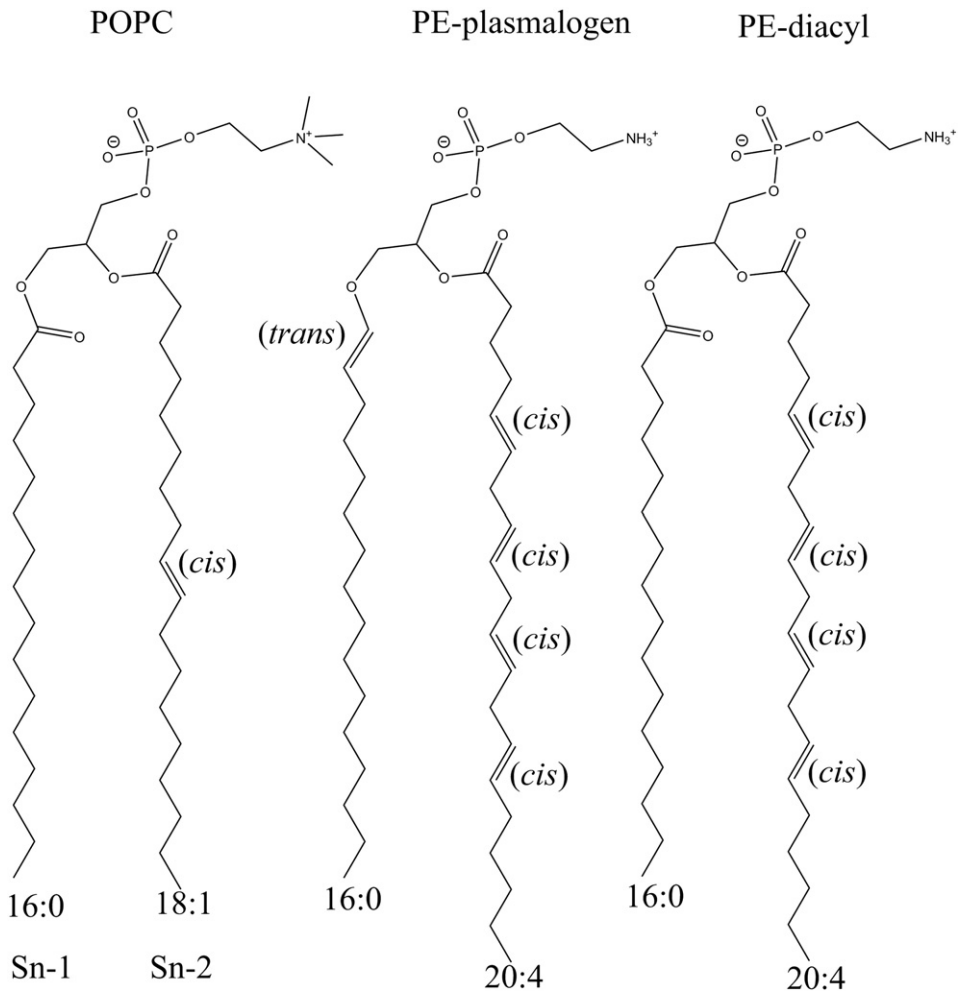

Fig. 1. The chemical structures for the POPC, PE–plasmalogen, and PE–diacyl lipid species. The chain lengths and saturation degree of the sn-1 and sn-2 chains are marked below the chemical structures.