Biophysical Chemistry 221 (2017) 1–9

Contents lists available at ScienceDirect

Biophysical Chemistry

journal homepage: http://www.elsevier.com/locate/biophyschem

Laurdan emission study of the cholesterol-like effect of long-chain alkylresorcinols on the structure of dipalmitoylphosphocholine and sphingomyelin membranes

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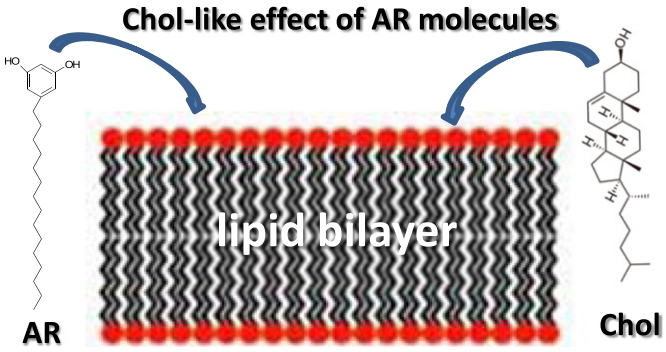
HIGHLIGHTS

- The cholesterol-like effect of ARs on DPPC and SM membranes
- High cooperativity of the phase lipid transition in ARs-mixed membranes
- The increase in Tm of ARs-mixed DPPC and SM membranes

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 5 August 2016
Received in revised form 6 November 2016
Accepted 10 November 2016
Available online 12 November 2016

Keywords:
Laurdan fluorescence
DPPC membranes
Sphingomyelin (SM)
Cholesterol
Long chain alkylresorcinols
Lipid main phase transition
Hydration of lipid membrane
Lipid chain order

ABSTRACT

Long-chain alkylresorcinols (ARs) are commonly found in plant and bacteria cells, and they exhibit a wide variety of biological effects, including antifungal, antitumor, and antiphrastic activities. The cholesterol (Chol)-like effect of ARs with hydrocarbon side-chain lengths ranging from C15 to C25 on the structure of pure and Chol-doped dipalmitoylphosphocholine (DPPC) and sphingomyelin (SM) membranes was investigated by Laurdan fluorescence spectroscopy. The Laurdan emission generalized polarization parameter was analyzed as a function of the temperature and excitation wavelength in DPPC (or SM)/Chol, DPPC (or SM)/AR, and DPPC/Chol/AR systems. It was found that AR incorporation into both DPPC and SM bilayers induces an increase in the temperature of the main lipid phase transition, similar to the effect of Chol molecule incorporation. The phase separation, lipid-chain ordering, and membrane hydration are discussed for the AR-mixed membranes and compared with DPPC (or SM)/Chol membranes.

1. Introduction

Cholesterol (Chol) is an abundant and essential lipid component of biological membranes [1]. Although Chol has several different functions in living cells, one of its main roles is as a modulator of the

Abbreviations: DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; SM, sphingomyelin; AR, alkylresorcinols; Chol, cholesterol; Tm, main phase transition; GP, generalized polarization parameter; FT-IR, Fourier-transform infrared spectroscopy.

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http://dx.doi.org/10.1016/j.bpc.2016.11.004
0301-4622/

physicochemical properties of the phospholipid bilayer structure of plasma membranes. One of the main effects of Chol insertion into a lipid membrane is connected with Chol-mediated changes in the temperature, which widens or even eliminates the main lipid phase transition [2,3]. Additionally, Chol is one of the main molecules responsible for the heterogeneous structure of biological membranes. There are indicators that prove that lipid rafts are Chol-rich domains with properties of the liquid-ordered (Lo) phase [4]. The structural properties of the Lo phase triggered by Chol molecules have been estimated in many studies based on a liposomal model of biological lipid membranes [2,5–7]. The Chol-rich Lo state is characterized by an increase in the lipid chain order, a restricted rate of lateral diffusion, a reduced area per molecule, and a decrease in membrane hydration.

Cholesterol not only plays an important role in biological membranes, it is also one of the crucial components of the lipid membrane of liposomes, which are used as a very effective drug delivery system. The presence of Chol molecules in the lipid membrane of liposomes increases the long-time stability of vesicles and prolongs their blood circulation time by decreasing the membrane permeability [8–10].

Searching for new chemical compounds with a Chol-like effect on the structure of lipid membranes is an interesting and important task for designing liposomal drug carriers. Chol molecules in the membrane wall of liposomes can be replaced by these new compounds, which can also have important biological functions. The resulting lipid membrane of the liposomes will have the same or similar structural properties to Chol-mixed membranes, but it will possess additional biological features related to the inserted compound.

In a presented work we discuss the Chol-like influence of long chain alkylresorcinolic (ARs) lipids on a structure of dipalmitoylphosphocholine (DPPC) membranes, see their structures in Fig. 1. DPPC lipids are one of the most numerous members of the most prevalent lipid group among those lipids constituting the basic structure of the lipid bilayer wall of liposomes [8,9]. Additionally, DPPC liposomes are frequently used as a model for lipid biomembranes [11–17].

Given that Chol molecules are located in sphingomyelin (SM) rafts, which are present in the biomembranes of living cells and rich in SM lipids, investigating the effect of AR molecules on SM membranes could provide information about whether AR molecules have a Chol-like effect on lipid biomembranes.

AR lipids with a wide range of biological activities naturally occur in plants, bacteria, fungi, and animals, but bran cereals are their main source. AR lipids possess antibiotic [18], antifungal [19], and antitumor [20] activities, which makes them attractive for the agriculture, pharmaceutical, and nutrition industries [21–24]. As an amphiphilic compound, they can easily interact with lipid membranes and change the properties and activities of various membrane-associated enzymes [25]. ARs are mainly found in the aleurone layers of the kernel [26]. Interestingly, they can replace phospholipids during encystment of *Azotobacter vinelandii* membranes [27]. All of the facts suggest that ARs can interact with biological lipid membranes, but their role in plant and bacterial cells is still not clear and needs further investigation. ARs are a common component of the diet of human and animals, and they can interact with their biomembranes. It has been suggested that AR compounds can be incorporated into erythrocyte membranes [28] and stored in adipocyte tissues as other lipids [29]. Nevertheless, the Chol-like effect of ARs on plant and animal physiology has not been reported. Studies presented in this paper show a Chol-like effect of ARs on a liposomal model of sphingomyelin rafts of biomembranes.

ARs can be used as part of novel liposomal formulations for drug delivery [30]. It has been shown that the presence of ARs in SM/Chol, PC,

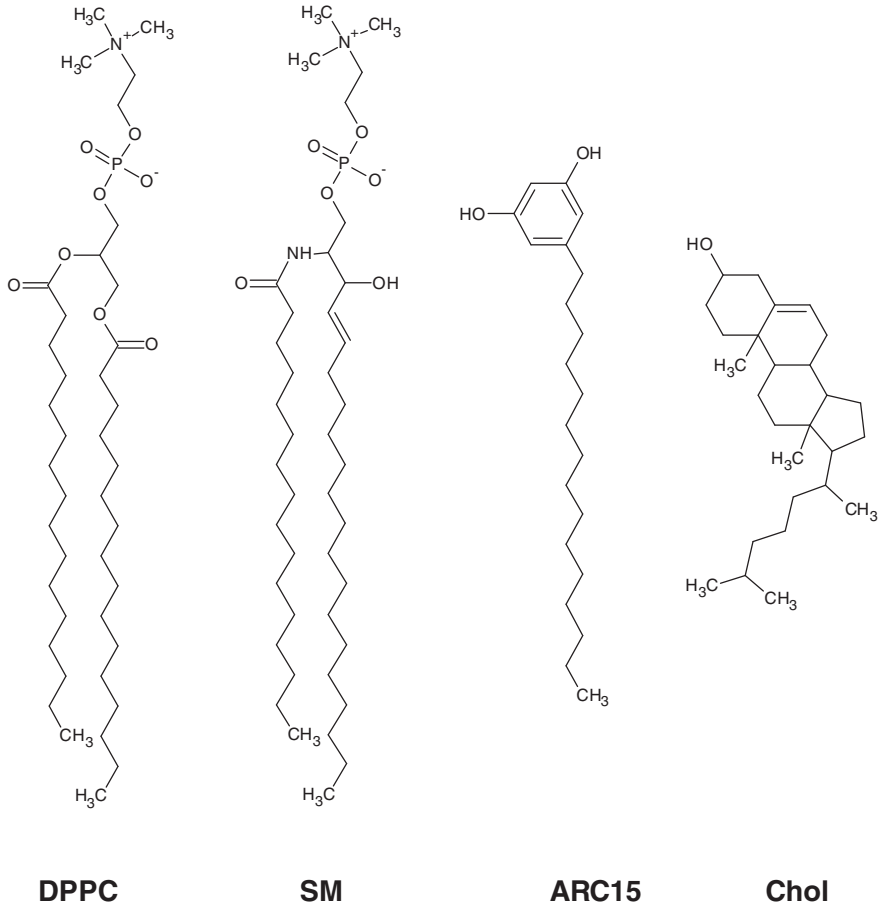

Fig. 1. Structure of DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine), SM (sphingomyelin), AR (15:0) (5-*n*-pentadecylresorcinol) and Chol (cholesterol). The AR homologs differ in the hydrocarbon side-chain length (C15–C25).