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Review

Cholesterol homeostasis and the escape tendency (activity) of plasma membrane cholesterol

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A B S T R A C T

We review evidence that sterols can form stoichiometric complexes with certain bilayer phospholipids, and sphingomyelin in particular. These complexes appear to be the basis for the formation of condensed and ordered liquid phases, (micro)domains and/or rafts in both artificial and biological membranes. The sterol content of a membrane can exceed the complexing capacity of its phospholipids. The excess, uncomplexed membrane sterol molecules have a relatively high escape tendency, also referred to as fugacity or chemical activity (and, here, simply *activity*). Cholesterol is also activated when certain membrane intercalating amphipaths displace it from the phospholipid complexes. Active cholesterol projects from the bilayer and is therefore highly susceptible to attack by cholesterol oxidase. Similarly, active cholesterol rapidly exits the plasma membrane to extracellular acceptors such as cyclodextrin and high-density lipoproteins. For the same reason, the pool of cholesterol in the ER (endoplasmic reticulum) increases sharply when cell surface cholesterol is incremented above the physiological set-point; *i.e.*, equivalence with the complexing phospholipids. As a result, the escape tendency of the excess cholesterol not only returns the plasma membrane bilayer to its set-point but also serves as a feedback signal to intracellular homeostatic elements to down-regulate cholesterol accretion.

Contents

Abbreviations: ER, endoplasmic reticulum; HDL, high-density lipoprotein; HMG-CoA reductase, hydroxy-3-methylglutaryl coenzyme A reductase; SR-BI, scavenger receptor class B type I.

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1. Introduction

Sterols are universal membrane constituents in eukaryotes. Nevertheless, they are not essential to membrane integrity, being rare among prokaryotes and scant in several of the eukaryotic organelles. Rather, they confer important properties on the plasma membrane and the endomembrane organelles with which the plasma membrane is in intermittent continuity [1,2]. Through their interactions with phospholipids and sphingolipids, sterols lower bilayer permeability by reducing the free volume created by the thermal motion of the fatty-acyl chains. For similar reasons, sterols condense bilayers, reduce their fluidity, compressibility and compliance and increase their mechanical strength [3]. As described in Section 2, sterols can enter into stoichiometric complexes with certain membrane phospholipids. These can drive the formation of functionally important bilayer phases, referred to as raft domains [1]. Sterols free of these phospholipid associations have a relatively high tendency to project from the bilayer (escape tendency or activity); this will be discussed in Section 3. Other properties of bilayer sterols in or free of phospholipid complexes will be taken up thereafter.

An early indication that there are two states of cholesterol activity in bilayers (*i.e.*, low and high escape tendency) was the conditionality of the susceptibility of membrane cholesterol to cholesterol oxidase attack. In particular, cholesterol in the outer leaflet of the red blood cell membrane was found to be resistant to this enzyme, while the cytoplasmic leaflet was quite sensitive [4]. It was then shown that this dichotomy corresponded to the asymmetrical composition of the membrane; that is, synthetic vesicles rich in endofacial lipids (namely, unsaturated phosphatidylethanolamines and phosphatidylserines) fostered the oxidation of cholesterol while the exofacial lipids, the more saturated sphingomyelins and phosphatidylcholines, did not [5]. Corresponding differences were later demonstrated for the rate and extent of transfer of cholesterol from synthetic vesicles; that is, sterol efflux was retarded by saturated phospholipid chains, phosphocholine head groups and, most of all, sphingolipids [6,7].

It was also found early on that the susceptibility of the membranes of intact red cells to cholesterol oxidase rose abruptly – from negligible to total – when the cholesterol content was incremented from just below to just above its physiologic level (Fig. 1). (Why a slight enrichment caused all of the sterol to become a substrate was a mystery then but is explained below.) Such observations lead to the working hypothesis that underlies this review: membrane cholesterol forms complexes with certain bilayer phospholipids. These complexes hold the cholesterol in a state of low escape tendency. Cholesterol oxidase acts preferentially on the uncomplexed cholesterol with a high escape tendency. For the same reason, bilayer cholesterol that is not complexed is more readily transferred to acceptors.

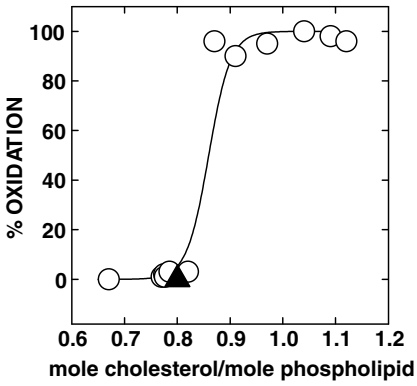

Fig. 1. Dependence of the susceptibility of cholesterol to cholesterol oxidase on red cell membrane cholesterol content near its resting level (▲). Replotted from Ref. [8].

2. Interactions of sterols with phospholipids

The fundamental properties of the phospholipids in bilayers are well understood [9], and their interactions with sterols have been extensively characterized [2,10]. The cholesterol molecule has a rigid, planar steroid nucleus comprised of four fused rings plus a terminal, flexible *iso*-octyl tail (Fig. 2). The sterol molecule aligns roughly parallel to its phospholipid neighbors in bilayers. Its 3-β-hydroxyl group resides in the vicinity of their fatty-acyl carbonyl groups near the aqueous interface. Sterols are not ideal solutes dissolved in the hydrophobic core of the bilayer. Rather, they associate with the more polar lipids with varied strengths of interaction [11]. What matters most in these associations is the length of the nonpolar chains of the polar lipids, the (un)saturation of their chains (*i.e.*, the number, position and orientation [*cis* versus *trans*] of their double bonds, and the size and structure of their polar head groups [10]). The smooth α-face of the sterol nucleus makes favorable van der Waals contacts with the saturated fatty-acyl chains of phospholipids down to about their tenth methylene group. Phospholipids with phosphocholine head groups interact more strongly with sterols than those with smaller head groups such as phosphatidylethanolamine and phosphatidylserine. Sterols prefer sphingomyelin to phosphatidylcholine; since these two classes of phospholipid have identical phosphocholine head groups, the difference is attributable to the longer and more saturated fatty-acyl tails of sphingolipids as well as to hydrogen bonding between the hydroxyl moiety of the sterol and the polar atoms in the lipid head group.

By themselves, phospholipids bearing two long and saturated fatty-acyl substituents typically form a close-packed, ordered (solid or gel) phase below their melting temperature. Their chains are well oriented toward the central plane of the membrane. Interaction with sterols reorganizes such bilayers into a distinctive liquid-ordered phase. In this state, the fatty-acyl chains remain aligned and extended parallel to the sterol nucleus, but the

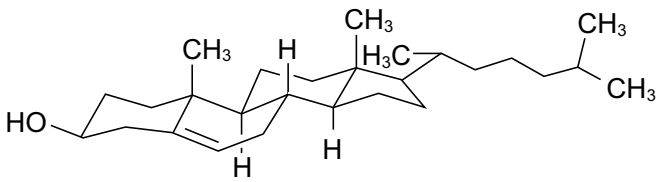

Fig. 2. The chemical structure of cholesterol. Note that the α-face of the nucleus (facing down) is "smooth" while the β-face (facing up) is made "rough" by the projection of methyl groups from carbons 10 and 13. Courtesy of Mark E. Duban.