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Review

Interactions of oxysterols with membranes and proteins

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ABSTRACT

Oxysterols are oxidized derivatives of cholesterol or by-products of cholesterol biosynthesis with multiple functions. Even though they are heterogeneous in their biological activities, they have the common property of transferring between membranes orders of magnitude faster than cholesterol, due to higher polarity and poorer membrane packing. Depending on the nature and location of the oxygen substitution, oxysterols have distinct impacts on the biophysical properties of membranes, including the formation of liquid ordered domains. This is suggested to explain differences in the cytotoxic potential of various oxysterols. Besides the effects of oxysterols on membrane biophysical properties, the endogenous cellular oxysterols are suggested to execute important functions via interactions with receptor proteins. Increasing evidence suggests that oxysterols act as ligands of liver X receptors, transcription factors with key roles in lipid metabolism. Oxysterols were also shown to interact with the Insig (insulin-induced gene) proteins, revealing a mechanism by which they regulate the transport and maturation of sterol-regulatory element binding proteins as well as the stability of a rate-limiting sterol biosynthetic enzyme. Furthermore, a number of other cellular receptors for oxysterols involved in cell signaling, lipid metabolism, and vesicle transport have been discovered, enhancing the interest in these compounds in several branches of biomedical research.

Contents

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Abbreviations: 4βOHC, 4β-hydroxycholesterol; 5,6EPOX, 5,6-epoxycholesterol; 7KC, 7-ketocholesterol; 7OHC, 7-hydroxycholesterol; 22(R)OHC, 22(R)-hydroxycholesterol; 24(S),25EPOX, 24(S),25-epoxycholesterol; 24(S)OHC, 24(S)-hydroxycholesterol; 25OHC, 25-hydroxycholesterol; ACAT, acyl-coenzyme A:cholesterol acyltransferase; EPOX, epoxycholesterol; ER, endoplasmic reticulum; HMGR, 3-hydroxy-3-methylglutaryl coenzyme A reductase; Insig, insulin-induced gene; KC, ketocholesterol; LCAT, lecithin:cholesterol acyltransferase; l_d, liquid disordered (domain); l_o, liquid ordered (domain); LDL, low-density lipoprotein; LXR, liver X receptor; NPC, Niemann-Pick C; OHC, hydroxycholesterol; ORP, OSBP-related protein; OSBP, oxysterol-binding protein; Oshp, OSBP homologue protein; PIP, phosphoinositide; PtdIns, phosphatidylinositol; SCAP, SREBP cleavage activating protein; SREBP, sterol regulatory element binding protein.

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1. Comparison of the biophysical properties of cholesterol and oxysterols

Cholesterol has a hydrophobic tetracyclic ring structure (sterol nucleus) with a β-hydroxyl group at position 3, and a branched iso-octyl side chain. The α-face of the cholesterol ring structure is flat, while the β-face is more bulky. Cholesterol orients in biological membranes roughly perpendicular to the bilayer plane so that the 3β-hydroxyl group is located at the membrane–water interface together with phospholipid head groups, and the iso-octyl side chain points at the hydrophobic interior of the bilayer (Fig. 1). The cholesterol ring structure tends to package tightly with the saturated fatty acyl/sphingosine chains of sphingolipids and glycerophospholipids. Due to this packing property, cholesterol is capable of condensing phospholipid membranes and facilitating the formation of liquid ordered (l_o) phases that are shown to co-exist with more fluid liquid disordered (l_d) phases at least under *in vitro* conditions (reviewed by Simons and Ikonen (2000), Maxfield and Tabas (2005)).

Oxysterols form a heterogeneous group of cholesterol-related molecules with additional oxygen substitutions: hydroxyl, carbonyl, epoxy, hydroperoxy, or carboxyl moieties. A common property for these modifications of cholesterol structure is that they make the molecules markedly more hydrophilic. Secondly, they can significantly change the 3-dimensional shape of the sterol, thus altering its lipid packing properties. Because of these two factors, oxysterols such as 7-ketocholesterol (7KC), 7β-hydroxycholesterol (7βOHC), 25-hydroxycholesterol (25OHC) and cholesterol hydroperoxides transfer spontaneously between membranes at rates orders of magnitude faster than cholesterol (Theunissen et al., 1986; Lange et al., 1995; Morel et al., 1996; Vila et al., 2001). Meaney et al. (2002) reported that the rate of oxysterol transfer from erythrocytes to plasma acceptors correlates with the distance between the 3β-hydroxyl group and the second oxygen function – in other words, species modified in the side chain transfer more rapidly than those oxygenated in the sterol nucleus, 4β-hydroxycholesterol (4βOHC) behaving very similar to cholesterol. Depending on the nature and location of the oxygen substitution, oxysterols have distinct effects on membrane lipid order and phase behaviour (Rooney et al., 1986; Theunissen et al., 1986; Verhagen et al., 1996; Wang et al., 2004; Massey and Pownall, 2006).

Due to thermodynamic constraints, the orientation of oxysterols in membranes (often studied in model monolayers) differs significantly from that of cholesterol. Oxysterols with oxygen substitutions in the side chain (mainly hydroxyl groups) have polar moieties at both ends of the molecule, favouring an orientation horizontal to the membrane surface (Fig. 1); under high surface pressure they may even adopt an inverted orientation where the side chain hydroxyl group is at the air–water interface (Kauffman et al., 2000). Under low surface pressure oxysterols modified at the 5-, 6-, or 7-positions of the sterol nucleus tend to adopt a tilted orientation positioning both of the polar functions close to the interface (Kauffman et al., 2000; Li et al., 2003; Massey and Pownall, 2005) (Fig. 1). Moreover, oxysterols modified in the sterol nucleus show clearly weaker membrane condensing activity than cholesterol (Rooney et al., 1986; Theunissen et al., 1986; Kauffman et al., 2000; Phillips et al., 2001). These observations suggest that oxysterols have the capacity to induce membrane surface

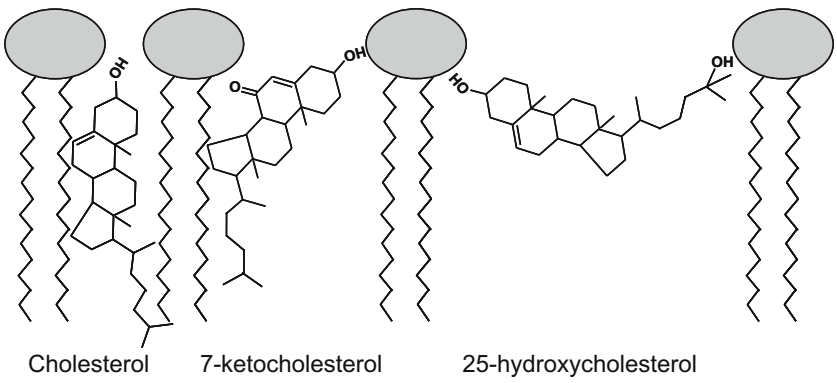

Fig. 1. Orientation of cholesterol and select oxysterols in a membrane – a schematic presentation. Cholesterol orients roughly perpendicular to the membrane plane. It has the ability to condense membranes and to organize sphingo/glycerophospholipids with saturated fatty acyl chains into l_o domains or rafts. 7-ketocholesterol tends to adopt a tilted orientation in the presence of l_d domain favouring lipids, and seems to have the ability to destabilize l_o domains. Under low surface pressure side-chain hydroxylated oxysterols such as 25-hydroxycholesterol may orient horizontally, and are suggested to expand membranes, but orient vertically under high surface pressure. The image is mainly based on the results by Kauffman et al. (2000) and Massey and Pownall (2005).