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Oxysterols: Influence on plasma membrane rafts microdomains and development of ocular diseases

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ABSTRACT

Oxidation of cholesterol into oxysterols is a major way of elimination of cholesterol from the liver and extrahepatic tissues, including the brain and the retina. Oxysterols are involved in various cellular processes. Numerous links have been established between oxysterols and several disorders such as neurodegenerative pathologies, retinopathies and atherosclerosis. Different components of the lipid layer such as sphingolipids, sterols and proteins participate to membrane fluidity and forme lipid rafts microdomains. Few data are available on the links between lipids rafts and oxysterols. The purpose of this review is to suggest the potential role of lipid rafts microdomains in the development of retinopathies with special emphasis and opening perspectives of their interactions with oxysterols. Actually cholesterol oxidation mechanism may have deleterious effect on its ability to support rafts formation .This review suggest that the effect of oxysterols of lipid rafts would probably depend on the oxysterol molecule and cell type.

1. Lipid rafts

Cell membranes present a high level of complexity of lipid and protein organization to perform the cell functions. The membrane lipid bilayer is not a passive structure but has the capability to laterally segregate different components: sphingolipids, sterols, proteins. This capability is based on dynamic membrane fluidity due to coexistence of specific liquid-ordered (Lo) and liquid-disordered (Ld) phases. The Lo phase is created by lipid raft microdomains enriched in cholesterol and saturated long acyl chain-containing phospholipids with low phosphatidylcholine. They are tightly packed together and present a high degree of lateral diffusion in the lipid bilayer. The lipid raft microdomains are resistant to non-ionic detergent and so called detergent-resistant membranes (DRM). There are two major subtypes of lipid rafts, namely caveolar and flat rafts [1,2]. Caveolae are small invaginations, approximately 50–100 nm in size, that are present in many mammalian cell types. Caveolae appear to be stabilized by the caveolin-1 protein, the main isoform found in non-muscle cells [3]. The caveolar rafts are rich in GM1 ganglioside. The second major subtype of lipid rafts, namely flat rafts, is co-planar and rich in GM3 ganglioside [4] (Fig. 1). Lipid rafts float in the membrane and are considered as signaling platforms that would be involved in several cellular mechanisms, notably in cell signaling, cell adhesion, cell migration, inflammation, in immune effector cells, and in the initiation of atherosclerotic plaque [5,6]. Regulation of these signaling pathways is dependent on raft composition. The binding of a ligand to its receptor has been shown to lead to the recruitment of ligand-receptor complexes in rafts and to trigger the signaling pathway. The binding of hormones or cytokines to their receptors lead the recruitment of receptor/ligand complexes in raft domains [7]. In contrast, recruitment of a protein in rafts can inhibit a signaling pathway by exclusion of the specific proteins from rafts [8]. Lipid composition and more particularly the level of cholesterol in plasma membrane is a major determinant of the localization or exclusion of proteins in rafts and also modulate signal transduction. In reconstituted models of membranes, the formation of these microdomains is dependent upon the chemical structure of sterols [9]. Sterols can be qualified as promoters or inhibitors of the formation of Lo phase. It is reported that most small modifications of cholesterol structure have moderate deleterious effects on the

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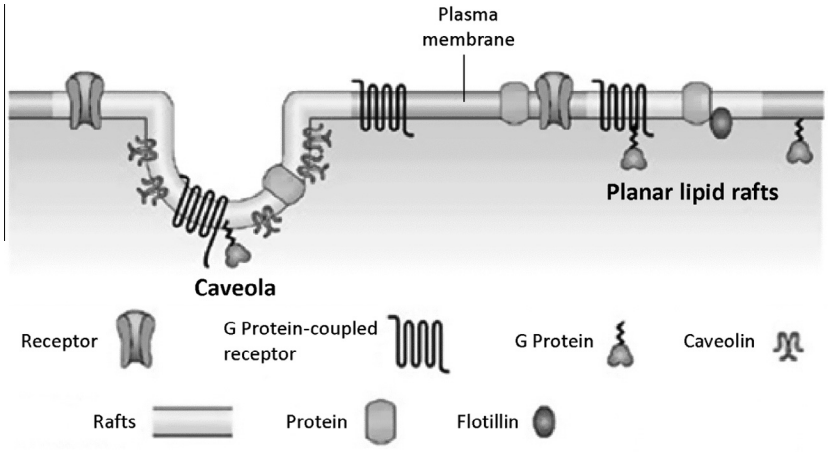

Fig. 1. Representation of rafts (from [97]). The rafts, planar or caveolar, segregate from other regions of the bilayer contains transmembrane proteins (P), Receptors, G protein-coupled receptor, are enriched in Cholesterol and saturated fatty acids. Caveolae are formed by self-associating caveolin molecules making a hairpin loop in the membrane, and planar rafts containing essentially Flotillin.

ability to support raft formation. Oxysterols generated by cholesterol oxidation can have different physicochemical properties and may be considered as potent modulators of lipid raft formation [10].

The purpose of the present paper is to review first the formation of oxysterols, their associations with neurodegenerative pathologies including those of the retina and then to suggest whether oxysterols may exert their biological functions via lipid rafts.

2. Oxysterols: general concerns

Hydroxycholesterols are a sub-group of oxysterols that encompass a large variety of 27-carbons oxidized derivatives of cholesterol. Oxidation is represented by either a hydroxyl, keto, hyperoxy, carbonyl or epoxy group, in addition to the genuine 3β-hydroxyl group of cholesterol. Oxidation takes place on the sterol core essentially at 4, 5, 6 and 7 positions or at 24, 25 and 27 position of the lateral chain which leads to a great diversity of oxysterols [11]. Oxysterols are found at much lower levels than cholesterol in mammalian tissues, and vary from one organ to the other. As an example, the concentration of 24S-hydroxycholesterol (24S-OHC) varies from 0.2 in heart or muscle, to 2.19 in the brain [12] or 3.4 μg per mg of cholesterol in the neurosensory retina [13]. Oxysterols originate from either exogenous dietary intake, and/or endogenous pathway by enzymatic or chemical reactions [14]. For example, 27-hydroxycholesterol (27-OHC), and 24S-OHC are produced by enzymatic pathway. Auto-oxidation processes generate for example, 7α-hydroxycholesterol (7α-OHC), 7β-hydroxycholesterol (7β-OHC) and 7-ketocholesterol (7KC) [15]. b7α-OHC and 25-hydroxycholesterol (25-OHC) may be produced by both enzymatic pathways and cholesterol auto-oxidation (Fig. 2). The physiologically most important oxysterols are produced in cells by mitochondrial or endoplasmic reticulum cytochrome P450 cholesterol hydroxylases that are present in several organs, such as the brain, liver and retina or cells such as macrophages [16]. Enzymatically formed oxysterols are transported by lipoproteins and albumin. They are also known to be endogenous

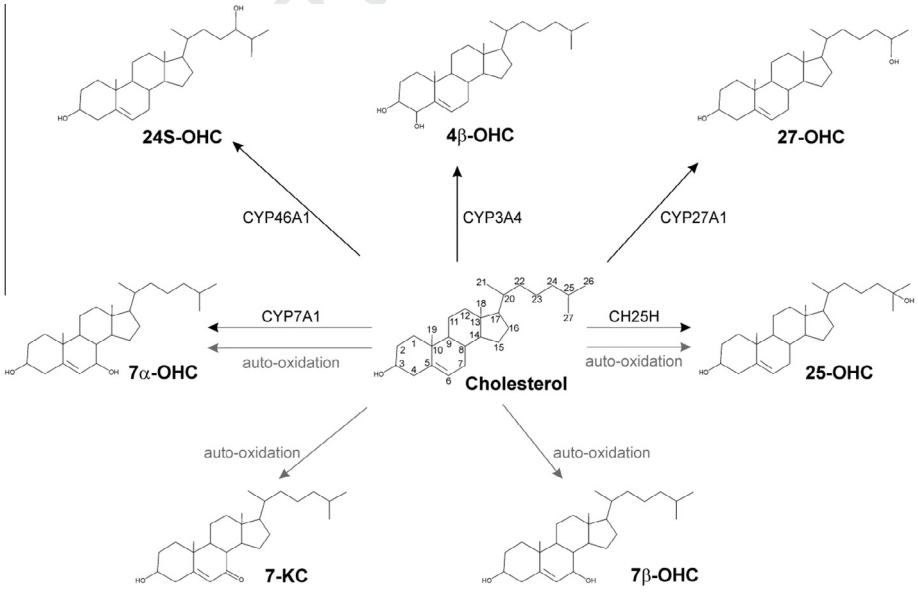

Fig. 2. Structure and origins of the major oxycholesterols. Numbering of carbons on cholesterol structure permit to identify the position of the oxygenated functions introduced on cholesterol structure. Some of oxysterols are enzymatically produced like 7α-hydroxycholesterol (7α-OHC) by CYP7A1, 4β-hydroxycholesterol (4β-OHC) by CYP3A4, 25-hydroxycholesterol (25-OHC) by CH25H, some are non-enzymatically produced like 7-ketocholesterol (7-KC), 7β-hydroxycholesterol (7β-OHC), or can be produced either by enzymatically or not pathway like 7α-hydroxycholesterol (7α-OHC) and 25-OHC. Name of enzyme are mentioned above the arrow.

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