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Review

Oxysterols: Sources, cellular storage and metabolism, and new insights into their roles in cholesterol homeostasis

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ABSTRACT

Oxysterols are structurally identical to cholesterol, but with one or more additional oxygen containing functional groups (such as alcohol, carbonyl or epoxide groups). The wide array of oxysterols encountered in human health and disease vary in their origin (either enzymic or non-enzymic), and their putative effects and/or function(s). Some are thought to be damaging, whereas others may play important physiological roles, including in the regulation of cholesterol homeostasis. In this review, we will concentrate on the major cellular oxysterols. We summarise their location, generation, metabolism and elimination, as well as providing insights into the latest research into their regulatory roles in cholesterol homeostasis.

Contents

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Abbreviations: 7OOHC, 7-hydroperoxycholesterol; 7αHC, 7α-hydroxycholesterol; 7βHC, 7β-hydroxycholesterol; 7KC, 7-ketocholesterol; 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 24,25EC, 24(*S*),25-epoxycholesterol; 24HC, 24(*S*)-hydroxycholesterol; 25HC, 25-hydroxycholesterol; 27HC, 27-hydroxycholesterol; ABCA1, ATP-binding cassette, subfamily A, member 1; ABCG1, ATP-binding cassette, subfamily G, member 1; ACAT, acyl CoA cholesterol acyl transferase; AcLDL, acetylated low density lipoprotein; apoAI, apolipoprotein AI; DOS, 2,3(*S*); 22(*S*), 23-dioxidosqualene; ER, endoplasmic reticulum; HDL, high density lipoprotein; HMG-CoA reductase, 3-hydroxy-3-methyl-glutaryl-CoA reductase; L_d, liquid disordered domain; Insig, insulin-induced gene; L_o, liquid ordered domain; LCAT, lecithin cholesteryl acyl transferase; LDL, low density lipoprotein; LXR, liver X receptor; MOS, 2,3(*S*)-monooxidosqualene; OSC, 2,3-oxidosqualene cyclase; OxLDL, oxidised LDL; ROS, reactive oxygen species; Scap, SREBP cleavage activating protein; SM, squalene monooxygenase; SR, scavenger receptor; SREBP, sterol regulatory element binding protein; SULT, sulfotransferase.

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1. Introduction

This volume reflects a recent renewed interest in oxysterols, a century after Lifshultz first identified 'oxycholesterol' (Lifschutz, 1913), and three decades after Kandutsch and colleagues proposed what has become known as the 'Oxysterol Hypothesis of Cholesterol Homeostasis' (Kandutsch et al., 1978). The revised interest in oxysterols probably arises from recent advances in our understanding of the importance of cholesterol in controlling eukaryotic membrane structure and function. Specific oxysterols have the potential to either control cholesterol biosynthesis and/or to directly interfere with normal cellular functions of cholesterol. The following chapters detail specific roles of oxysterols in lipid homeostasis and signalling, as well as potentially deleterious effects on cell function and their pathobiology. In this review, we will focus on cellular oxysterols, their location, generation, metabolism and elimination. For details of plasma oxysterols, the reader is directed to several earlier detailed reviews (Brown and Jessup, 1999; Schroepfer, 2000).

2. Biological sources of oxysterols

Oxysterols are largely derived from cholesterol by a variety of routes. Several previous reviews have comprehensively discussed the major biological oxysterols and the routes for their formation (Brown and Jessup, 1999; Schroepfer, 2000; Gill et al., 2008; Smith and Murphy, 2008). Fig. 1 shows the structures of several major biological oxysterols and their relationship to the structure of cholesterol. In general, biological oxysterols fall into two main categories; those oxygenated on the sterol ring, mainly at the 7-position (e.g., 7α/β-hydroperoxycholesterol (7OOHC), 7-ketocholesterol (7KC) and 7α/β-hydroyxcholesterol (7HC)) and those oxygenated on the side-chain (e.g., 24*S*-hydroxycholesterol (24HC), 25-hydroxycholesterol (25HC) and 27-hydroxycholesterol (27HC)). Generally, ring-oxygenated sterols tend to be formed non-enzymically, whereas side-chain oxygenated sterols usually have an enzymic origin. However, there are exceptions to this rule; for example 25HC and 7αHC can be produced by both enzymic and non-enzymic routes (see Gill et al., 2008 for further discussion).

2.1. Non-enzymic oxidation

Direct radical attack on cholesterol by reactive oxygen species (ROS), such as the hydroxyl radical, leads to abstraction of an allylic hydrogen atom at C-7. The carbon-centred radical generated at C-7 is relatively long-lived and can react further with molecular oxygen to form a cholesterol peroxyl radical ($COO^{\cdot}$). Further hydrogen abstraction from another lipid generates the relatively stable cholesterol hydroperoxides (7α- and 7β-OOHC) (Fig. 1). Cholesterol hydroperoxides have been detected at low levels in some biological samples, including human atherosclerotic plaque (Chisolm et al., 1994; Brown et al., 1997; Adachi et al., 2000). 7OOHC is the major oxysterol formed at the early stages of non-enzymic oxidation of cholesterol (Brown et al., 1997). However, tissue levels of 7OOHC are usually quite low relative to downstream 7-oxygenated products, most probably due to the further processing of the hydroperoxides both by further non-enzymic lipid oxidation as well as by enzymic reduction (Brown et al., 1997). In the presence of trace levels of transition metals, cholesterol hydroperoxides are further decomposed non-enzymically to 7α/β-alkoxy radicals ($CO^{\cdot}$), which in turn can undergo further reactions to generate 7α/β-hydroxycholesterols and 7-ketocholesterol (Fig. 1). These are the major non-enzymically generated oxysterols that are present in most tissues (Brown and Jessup, 1999).

The major locations of cholesterol are in plasma lipoproteins and in cell membranes, where cholesterol is invariably present together with other lipids, predominantly phospholipids. Cholesterol is chemically less susceptible to oxidative attack than the polyunsaturated fatty acyl moieties present in phospholipids. This is seen in *in vitro* oxidation of cholesterol in plasma and in isolated low density lipoprotein (LDL), where oxidation of fatty acyl groups occurs earlier and more extensively than that of cholesterol (Noguchi et al., 1998). This means that, in these situations, oxysterols occur in a generally oxidised milieu, and will be accompanied by many other, potentially toxic, oxidised compounds. This is an important consideration when the biological activities of complex species such as oxidised LDL (OxLDL) are measured. Interestingly, a recent study of the kinetic of lipid oxidation in cultured cells exposed to oxidative stress reported that cholesterol was relatively more oxidised than polyunsaturated fatty acids (Saito et al., 2007). On the face of it, this suggests that cholesterol in cell membranes is