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Review

Cytotoxic effects of oxysterols associated with human diseases: Induction of cell death (apoptosis and/or oncosis), oxidative and inflammatory activities, and phospholipidosis

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ABSTRACT

Oxysterols resulting from spontaneous or enzymatic oxidation of cholesterol are present in numerous foodstuffs and have been identified at increased levels in the plasma and the vascular walls of patients with cardiovascular diseases, especially in atherosclerotic lesions. Consequently, their role in lipid disorders is widely suspected, but they may also contribute to the development of important degenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, osteoporosis, age-related macular degeneration, and cataract. Since these pathologies can be associated with the presence of apoptotic cells, oxidative and inflammatory processes, and lipid disorders, the ability of oxysterols to trigger cell death, activate oxidation and inflammation, and modulate lipid homeostasis is being extensively studied. There are several important considerations regarding the physiological/pathophysiological functions and activities of the different oxysterols. It is therefore important to determine their biological activities and identify their signaling pathways, when they are used either in isolation or as mixtures. In these conditions, oxysterols may have cytotoxic, oxidative, and/or inflammatory effects, or no effects whatsoever. Moreover, with cytotoxic oxysterols, a substantial accumulation of polar lipids in cytoplasmic multilamellar structures was observed, demonstrating that cytotoxic oxysterols were phospholipidosis inducers. This basic knowledge on oxysterols contributes to a better understanding of the associated pathologies, so that new treatments and drugs can be designed.

Contents

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Abbreviations: AIF, apoptosis inducing factor; Akt/PKB, protein kinase B; AP-1, activator protein 1; ABCA1, ATP-binding cassette A1; COX, cyclooxygenase; Endo-G, endonuclease-G; ICAD, inhibitor of caspase-activated DNase; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; JNK, Jun-NH_2-terminal kinase; LC3, light chain 3; LDLs, low sensity lipoproteins; LPS, lipopolysaccharide; LXR, liver X-receptor; MAPK, mitogen-activated protein kinase; MIP-1β, macrophage inflammatory protein 1β; MnSOD, manganese superoxide dismutase; NAD(P)H oxidase, nicotinamide adenine dinucleotide phosphate-oxidase; NK, natural killer; OSBP, oxysterol-binding protein; oxLDLs, oxidized low-density lipoproteins; PARP, poly(ADP-ribose)polymerase; PDK-1, 3-phosphoinositide-dependent protein kinase-1; PLA_2, phospholipase A_2; ROS, reactive oxygen species; SDF-1α, stromal cell-derived factor; SREBP, sterol regulatory element binding protein; TNF, tumor necrosis factor; UPR, unfolded protein response.

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1. Chemical structures and origins of oxysterols

Oxysterols are 27-carbon-atom cholesterol oxidation products resulting from either the spontaneous or enzymatic oxidation of oxysterols (Addis, 1986; Smith, 1987, 1990; Guardiola et al., 2002; Jessup and Brown, 2005). Cholesterol is composed of three regions: a hydrocarbon tail (also called the lateral chain), a ring structure region with four hydrocarbon rings (A, B, C, and D), and a hydroxyl group. Oxidation can occur on the ring structure and on the lateral chain. The double bond present on the B hydrocarbon ring can be the target of free radical attacks, and therefore positions 4, 5, 6, and 7 are the most sensitive sites of spontaneous oxidation. The autoxidation of cholesterol on the B hydrocarbon ring leads to the formation of 7α- and 7β-hydroxycholesterols, 7-ketocholesterol, a good marker of autoxidation (Dyer et al., 1997), 5α,6α-epoxycholesterol, 5β,6β-epoxycholesterol, and cholestan-3β,5α,6β-triol (Patel et al., 1996). It is noteworthy that introducing an oxygen function increases the rate of cholesterol degradation into more polar compounds, and oxysterols with additional oxygen functions on the lateral chain can therefore be easily transported out of cells and eliminated.

Oxysterols are known to be present in various foodstuffs, notably cholesterol-rich foods such as dairy products, milk, eggs, dried egg powder, clarified butter (or ghee), meat products, and dried or stored fish (Przygonski et al., 2000; Boselli et al., 2001; Guardiola et al., 2002; Valenzuela et al., 2003). Generally, products containing cholesterol are susceptible to oxidation, especially those which are dehydrated, subjected to radiation, or submitted to high temperatures, as well as those that are cooked in the presence of oxygen (Yan, 1999; Leonarduzzi et al., 2002; Mazalli and Bragagnolo, 2007). Indeed, in these conditions, alimentary cholesterol is exposed to numerous reactive oxygen species (ROS) such as singlet oxygen (O_2^{-}), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\cdot}$), and ozone (O_3). Consequently, when food is stored for lengthy periods but not vacuum-packed, the generation of oxysterols markedly increases (Leonarduzzi et al., 2002). The most commonly detected oxysterols in processed foods are 7-oxygenated sterols (7-ketocholesterol, 7α-hydroxycholesterol, 7β-hydroxycholesterol) and 5,6-oxygenated sterols (5α,6α-epoxycholesterol, 5β,6β-epoxycholesterol, cholestan-3β,5α,6β-triol), as well as 25-hydroxycholesterol, 19-hydroxycholesterol, 20α-hydroxycholesterol, 3β-hydroxy-5α-cholestan-6-one, and 3β,5α-dihydroxycholestan-6-one, which are present in smaller amounts (Addis et al., 1996). Food oxysterols are mainly absorbed as esters in the intestinal tract and further transported in the plasma by chylomicrons. Interestingly, contrary to 7β-hydroxycholesterol, 7-ketocholesterol is only slightly absorbed (Linseisen and Wolfram, 1998) and rapidly metabolized in the liver (Lyons and Brown, 1999; Lyons et al., 1999; Schweizer et al., 2004). Furthermore, in plasma, oxysterols are transported by lipoproteins.

The highest levels of oxysterols are present in low-density lipoproteins (LDLs) and to a lesser extent in high-density lipoproteins (HDLs) and very-low-density lipoproteins (VLDLs) (Babiker and Diczfalusy, 1998). Some studies also showed that the oxysterols can be transported by albumin (Babiker and Diczfalusy, 1998). Compared to cholesterol, oxysterols are absorbed more quickly in the intestines, they have a faster plasmatic clearance, and they are quickly collected by tissues (Krut et al., 1997). It should be noted that cholesterol autoxidation can also take place in various tissues, most particularly in the arterial wall, during the atheromatous process (Berliner and Heinecke, 1996; Colles et al., 2001).

The ability of tissues to promote oxysterol synthesis was reported for the first time by Frederickson and Ono in 1956. They incubated radiomarked cholesterol with a subcellular fraction enriched in mitochondria, showing that 25-hydrocholesterol and 26-hydrocholesterol were formed Frederickson and Ono, 1956. The enzymatic synthesis of another oxysterol, 24-hydroxycholesterol, was described much later by Lin and Smith (1974). Since even a minor oxidation of cholesterol during sample processing would yield a substantial increase in oxysterol levels, isotopic methods combined with gas chromatography and mass spectrometry were developed to avoid artifactual results (Breuer and Björkhem, 1995; Diczfalusy, 2004). Consequently, it is now recognized that among the oxysterols found in the blood, some, such as 7α-hydroxycholesterol, 24S-hydroxycholesterol, 25-hydroxycholesterol, and 27-hydroxycholesterol, can result from enzymatic synthesis. The microsomal cytochrome P450 system is largely responsible for the enzymatic generation of endogenous oxysterols, including hepatic 7α-hydroxycholesterol (catalyzed by CYP7A1), 24S-hydroxycholesterol in brain and retina (catalyzed by CYP46), and 27-hydroxycholesterol in most tissues (catalyzed by CYP27), whereas the minor oxysterol, 25-hydroxycholesterol, is generated by the non-heme iron protein enzyme, cholesterol 25-hydroxylase (Lund et al., 1998; Ogishima et al., 1987; Björkhem and Diczfaluzsy, 2002; Souidi et al., 2004; Bretillon et al., 2007; Vaya and Schipper, 2007). In the hepatocytes, 27-hydroxylase (CYP27A1) and 7α-hydroxylase (CYP7A1) are two key enzymes of bile acid biosynthesis (Björkhem, 1992; Javitt, 1990), and the enzyme CYP7A1 is the limiting enzyme in the conversion of cholesterol into bile acids (Li and Spencer, 2000). The enzyme CYP27A1 also catalyzes the addition of a hydroxyl group not only on cholesterol to give 27-hydroxycholesterol, but also on intermediates in bile synthesis such as 5β-cholestan-3α,7α,12α-triol and 5β-cholestan-3α,7α-diol to produce their hydroxylated forms at position 27 (Russell, 2000). Under treatment with phenobarbital, hepatic production of 4β-hydroxycholesterol resulting from the activation of the CYP3A4 enzyme has also been described (Bodin et al., 2001).