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Review

Cholesterol-5,6-epoxides: Chemistry, biochemistry, metabolic fate and cancer

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ABSTRACT

In the nineteen sixties it was proposed that cholesterol might be involved in the etiology of cancers and cholesterol oxidation products were suspected of being causative agents. Researchers had focused their attention on cholesterol-5,6-epoxides (5,6-ECs) based on several lines of evidence: 1) 5,6-ECs contained an oxirane group that was supposed to confer alkylating properties such as those observed for aliphatic and aromatic epoxides. 2) cholesterol-5,6-epoxide hydrolase (ChEH) was induced in pre-neoplastic lesions of skin from rats exposed to ultraviolet irradiations and ChEH was proposed to be involved in detoxification processes like other epoxide hydrolases. However, 5,6-ECs failed to induce carcinogenicity in rodents which ruled out a potent carcinogenic potential for 5,6-ECs. Meanwhile, clinical studies revealed an anomalous increase in the concentrations of 5,6β-EC in the nipple fluids of patients with pre-neoplastic breast lesions and in the blood of patients with endometrious cancers, suggesting that 5,6-ECs metabolism could be linked with cancer. Paradoxically, ChEH has been recently shown to be totally inhibited by therapeutic concentrations of tamoxifen (Tam), which is one of the main drugs used in the hormonotherapy and the chemoprevention of breast cancers. These data would suggest that the accumulation of 5,6-ECs could represent a risk factor, but we found that 5,6-ECs were involved in the induction of breast cancer cell differentiation and death induced by Tam suggesting a positive role of 5,6-ECs. These observations meant that the biochemistry and the metabolism of 5,6-ECs needed to be extensively studied. We will review the current knowledge and the future direction of 5,6-ECs chemistry, biochemistry, metabolism, and relationship with cancer.

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1. Introduction

Cholesterol is a tetracyclic lipid of growing biological importance since its discovery by François Poulletier de la Salle in 1758 and was first named cholesterine by Christian Chevreul in 1815 [1]. Since the last century cholesterol is known to be subject to oxidation leading to the formation of mono- or poly-oxygenation products called oxysterols. The main functional groups containing oxygen atoms are epoxides, ketones, hydroxyl and peracids [2]. Oxysterols are produced through enzymatic reactions reflecting the existence of a metabolic pathway and are also produced by autoxidation through non-enzymatic mechanisms, which are associated with inflammatory-linked pathologies [2]. It is however interesting to note that most oxysterols can be produced through chemical reactions and were discovered by chemists and biochemists before the enzymes responsible for their biosynthesis were characterized [3–5]. Among these oxysterols, 5,6-ECs have stimulated the interest of researchers some years after the photo-oxidation products of cholesterol were suspected to be involved in photo-carcinogenesis [6]. Because of the presence of an oxirane group, it was supposed that 5,6-ECs could be electrophilic and behave like alkylating agents with direct carcinogenic properties. Recent data from literature ruled out that 5,6-ECs could be direct alkylating substances [7] and provides evidence that 5,6-ECs may be involved in physiological processes that result in metabolites with tumor promoter properties as well as to the production of steroidal alkaloids which are anti-oncogenic.

Abbreviations: AEBS, antiestrogen binding site; ChEH, cholesterol epoxide hydrolase; Tam, tamoxifen, trans-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethylamine; D8D7I, 3β-hydroxysterol-Δ^8-Δ^7-isomerase; DHCR7, 3β-hydroxysterol-Δ^7-reductase; cholesterol, cholest-5-en-3β-ol; 5,6-EC, 5,6-epoxy-cholesterol; CT, cholestane-3β,5α,6β-triol; 5,6α-EC, 5,6α-epoxy-5α-cholestestan-3β-ol; 5,6β-EC, 5,6β-epoxy-5β-cholestestan-3β-ol; 5,6-ECS, 5,6α-epoxy-5α-cholestestan-3β-sulfate; LXRα, Liver-X-Receptor alpha; LXRβ, Liver-X-Receptor beta; SULT2B1, Steroid sulfotransferase 2B1.

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2. Nomenclature, structure and reactivity of Cholesterol-5,6-epoxides (5,6-ECs)

2.1. Nomenclature of 5,6-ECs

Cholesterol-5,6-epoxides (5,6-ECs) are products of the oxidation of cholesterol at the Δ5 double bond between C5 and C6 of the B ring of the steroid backbone (Fig. 1A, 1–4). Two diastereoisomers or epimers exist: cholesterol-5alpha,6alpha-epoxide (5,6α-EC) and cholesterol-5beta,6beta-epoxide(5,6β-EC) (Fig. 1B). Their common names given by the lipid maps organization (www.lipidmaps.org) are 5,6α epoxy-cholesterol (lipid maps ID: LMST01010011) and 5,6β epoxy-cholesterol (lipid maps ID: LMST01010010). Their systematic names are 5,6α-epoxy-5α-cholestan-3β-ol and 5,6β-epoxy-5β-cholestan-3β-ol. However a lot of publications used different names which renders difficult an exhaustive bibliography on 5,6-ECs. For example, trivial names used (that do not take into account their stereochemistry) are: epoxy-cholesterol, cholesterol oxide and cholesterol epoxide. Other names can be found in the PubChem database at pubchem.ncbi.nlm.nih.gov (5,6α-EC: CID 108109; 5,6β-EC: CID 227037).

2.2. Structure of 5,6-ECs

5,6α-EC and 5,6β-EC are different by virtue of the oxygen of the epoxide ring being on the alpha side or on the beta side of the steroid core (Fig. 1B). The common structural representation of 5,6-EC diastereoisomers (Fig. 1B) suggests a dramatic conformational difference between 5,6α-EC and 5,6β-EC. However, our recent experimental data led us draw different conclusions. The A, C and D rings are identical in both 5,6-ECs and are in a chair conformation. The B ring of both 5,6-ECs is twisted with a different distortion at the junction of the A and B rings. In 5,6α-EC the angle C1-C10-C9 is 110.91° and the angle C4-C5-C6 is 120.23° whereas in 5,6β-EC these angles are 106.68° and 119.21° respectively. The conformational differences are highlighted through the superimposition of the 5,6-ECs [7]. We measured a displacement of 0.68 Å of the oxygen from the hydroxyl in C3 and a displacement of 0.83 Å of the C19 methyl groups. The van der Waals volume of the steroid backbone of 5,6-ECs was 241.84 $Å^3$ for 5,6α-EC and 242.16 $Å^3$ for 5,6β-EC. The difference in the van der Waals volume after superimposition of the 5,6-ECs was 22.19 $Å^3$, showing that 5,6α-EC and 5,6β-EC have 87% of their van der Waals volume in common but there was a 13% difference at the level of ring A, of the methyl C19 and of the epoxide ring from 5,6α-EC. The calculation of the total energy of the 5,6-ECs showed that 5,6β-EC is in a lower energy state and thus more stable than 5,6α-EC (ΔE = 15.1 kcal/mol). These data constitute the first experimental evidence of the existence of conformational differences between 5,6α-EC and 5,6β-EC. We observed less difference in the conformations of the 5,6-ECs in solution than that observed in the solid state [7], showing that the bending of the rings at the A, B junction was also less in solution than in the solid state.

2.3. Reactivity of 5,6-ECs

The reactivity of the 5,6-ECs has mainly been studied with 5,6α-EC and is summarized in Fig. 2A, with 5,6β-EC being marginally reactive or giving a mixture of products under forced conditions.

In acidic aqueous media 5,6-ECs can give cholestane-3β,5α,6β-triol (CT) as a single product of hydration [8]. In the presence of 37% hypochloric and 48% hypobromic acid, 5,6α-EC can produced 6β-chloro- and 6β-bromo-cholestan-3β,5α-diol and 6β-fluoro-cholestan-3β,5α-diol is obtained by reaction of 5,6α-EC with boron trifluoride etherate [9,10]. In gastric juice, which contains hydrochloric acid, 5,6α-EC and 5,6β-EC converted respectively to 6β-chloro-cholestan-3β,5α-diol and 5α-chloro-cholestan-3β,6β-diol and then both compounds gave CT [11]. 5,6α-EC can be hydrogenated in acetic acid with a palladium catalyst to give cholestane-3β,5α-diol, cholestane-3β-ol and cholestane-3β,5,6-triol [12]. In nucleophilic conditions, 5,6α-EC-3β-acetate, in the presence of acetonitrile and boron trifluoride etherate gave the

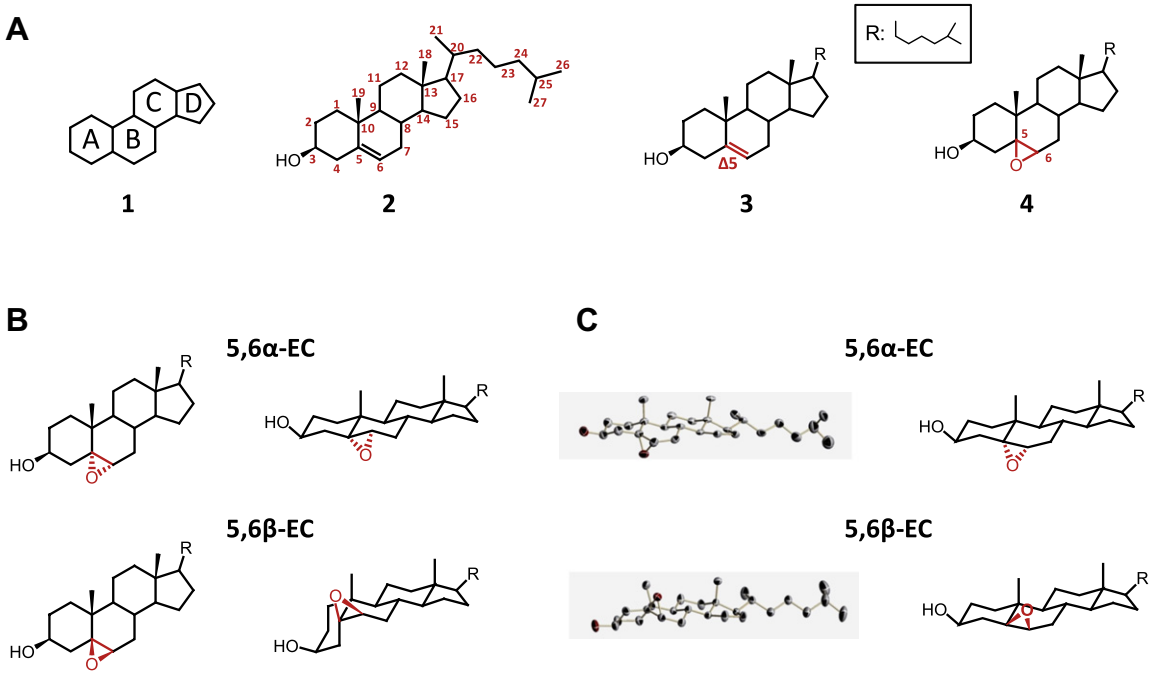

Fig. 1. Structure of 5,6-ECs. A) 1) Ring numbering of the tetracyclic steroid frame; 2) numbering of carbon atoms of the sterol nucleus and side chain; 3) positioning of the C5-C6 double bond; 4) representation of 5,6-ECs; B) Commonly used 2D representation of 5,6α-EC and 5,6β-EC epimers; C) Solid-state structure of 5,6α-EC and 5,6β-EC epimers as established by X-ray analysis and 2D representation of both diastereoisomers.

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