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- Review -

Function of 27-Hydroxycholesterol in Various Tissues and Diseases

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Oxysterols are oxygenated metabolites of cholesterol generated by serial enzymatic reactions during bile acid synthesis. Similar to cholesterol, oxysterols move rapidly to the intracellular region and modulate various cellular processes, such as immune cell responses, lipid metabolism, and cholesterol homeostasis. Different nuclear transcription factors, such as glucocorticoid, estrogen, and liver X receptors, can be modulated by oxysterols in multiple tissues. The most abundant oxysterol, 27-hydroxycholesterol (27-OHC), is a well-known selective modulator that can either activate or suppress estrogen receptor activity in a tissue-specific manner. The contribution of 27-OHC in atherosclerosis development is apparent because a large amount of it is found in atherosclerotic plaques, accelerating the transformation of macrophages into foam cells that uptake extracellular modified lipids. According to previous studies, however, there are opposing opinions about how 27-OHC affects lipid and cholesterol metabolism in metabolic organs, including the liver and adipose tissue. In particular, the effects of 27-OHC on lipid metabolism are entirely different between *in vitro* and *in vivo* conditions, suggesting that understanding the physiology of this oxysterol requires a sophisticated approach. This review summarizes the potential effects of 27-OHC in atherosclerosis and metabolic syndromes with a special discussion of its role in metabolic tissues.

Key words : Adipose tissue, atherosclerosis, Estrogen receptor (ER), 27-hydroxycholesterol (27-OHC), liver

Cholesterol and 27-hydroxycholesterol as an Oxysterol Derivative

Cholesterol metabolism

Cholesterol is a fat-like substance that is part of animal cells. It is a critical molecule for making cell membranes, hormones, bile acids, and vitamin D, which are involved in various metabolic processes [5, 6]. The mevalonate pathway, also known as the isoprenoid pathway, is an essential metabolic process responsible for cholesterol synthesis. More than 20 enzymatic reactions convert acetyl-CoA molecules to isopentenyl 5-diphosphate (IDP), an isoprenoid and sterol precursor [21]. As a rate-limiting step in cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase catalyzes the conversion of HMG-CoA to mevalonate. Statins, known as HMG-CoA reductase inhibitors, are classic cholesterol-lowering drugs that can reduce the risk of atherosclerotic cardiovascular disease [16]. In addition to HMG-CoA reductase, most of the genes regulating the mevalonate pathway, such as farnesylpyrophosphate synthase (FPPS), squalene synthase (SQS), and dehydrocholesterol reductase (DHCR4) are regulated by sterol regulatory element binding protein-2 (SREBP-2).

Sterol regulatory element binding proteins (SREBPs) were identified as a subfamily of basic helix-loop-helix leucine zipper (bHLH-LZ) transcription factors, which regulate gene expression involved in cholesterol biosynthesis and the low-density lipoprotein receptor (LDLR) pathway [4]. The three isoforms are encoded by two different genes. SREBP-1a and SREBP-1c primarily modulate the fatty acid synthetic pathway, and SREBP-2 is a master regulator of cholesterol metabolism [10, 31]. The N- and C-termini of SREBPs project into the cytosol, and are separated by a short loop that projects into the endoplasmic reticulum (ER) lumen (Fig. 1A). Several proteolytic cleavages are required for SREBP activation. In general, the C-terminal domain of SREBP-2 interacts with SREBP cleavage-activating protein (SCAP). To hold SREBP-2 in the ER membrane, the N-terminal domain of SCAP binds to ER-resident insulin-induced gene proteins

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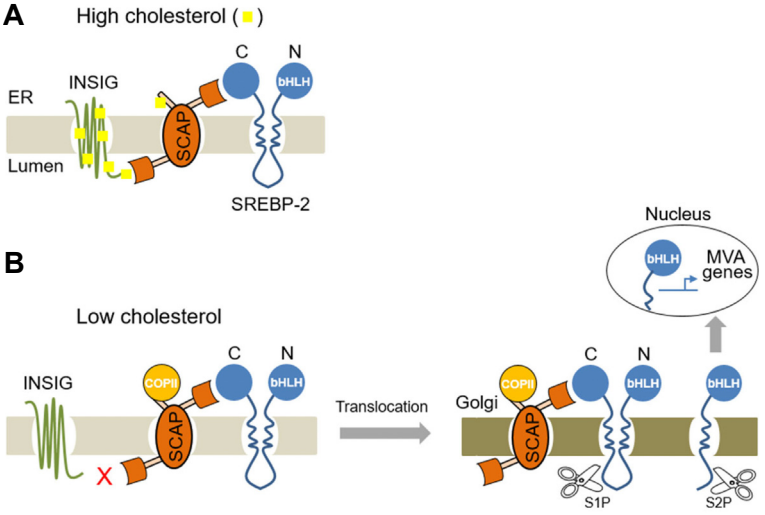

Fig. 1. SREBP activation pathway. (A) At high cholesterol levels, the SREBP precursor interacts with SCAP in ER membranes. INSIG binds to SCAP/SREBP complex to prevent release from the ER. (B) In cholesterol-deprived conditions, INSIG is degraded. This involves translocation of the SCAP/SREBP complex to the Golgi apparatus, where proteolytic cleavage of SREBP occurs. Once released from Golgi membranes, transcriptionally active fragments of SREBPs move to the nucleus and activate the transcription of cholesterol synthetic pathway.

(INSIG). Thus, these INSIG/SCAP/SREBP-2 complexes exist in the ER region to prevent the proteolytic process of SREBP-2 under cholesterol-enriched conditions [41]. In cholesterol-deprived cells, SCAP is released from INSIGs, which enhances the fusion of SCAP/SREBP into coatomer protein II (COPII)-coated vesicles, in turn delivering the cargo complex to the Golgi apparatus [25, 34](Fig. 1B). In the Golgi, SREBP-2 is cleaved sequentially by membrane-bound proteases, namely site-1 protease (S1P) and site-2 protease (S2P), to release the transcriptionally active form of SREBP-2 into the cytosol. After translocation to the nucleus, active SREBP-2 recognizes the sterol regulatory element region in the promoter of genes encoding enzymes involved in the cholesterol synthetic MVA pathway [19].

Effects of 27-hydroxycholesterol on atherosclerosis

Oxysterols are cholesterol derivatives containing additional hydroxyl groups or a keto group in cholesterol [3]. In general, cells convert cholesterol to bile acids or steroids, and many kinds of oxysterols originate in this process as intermediates [29]. To make these intermediates, oxidoreductases (cytochrome P450), hydrolases (cholesterol esterase), or transferases (hydroxysteroid sulfotransferases) are involved [22]. In addition, oxysterols can be formed by free radical oxidation of cholesterol, which is called autoxidation [11]. Importantly, oxysterols are involved in pathophysiological processes, such as regulation of the immune response, cholesterol metabolism, atherosclerosis, and neurodegenerative diseases [7, 33, 40]. Formation of oxysterols can be divided into two classes. Oxidoreductases (cytochrome P450), hydrolases (cholesterol esterase), and transferases (hydroxysteroid sulfotransferases)-induced enzymatic reaction on cholesterol. In particular, cytochromes CYP7A1, 27A1, 11A1, and 46A1 play critical roles to make 7a-hydroxycholesteorl, 27-hydroxycholesteorl, pregenolone, and 24S-hydroxycholesteorl respectively. As non-enzymatic methods, certain oxysterols are created by radical oxidation, which include 7-ketocholesterol, 5,6α-epoxycholesterol, 7β-hydroxycholesterol, and cholestane-3β,5α,6β-triol (Fig. 2). As mentioned above, three major oxysterols (27-, 24-, and 7α-hydroxycholesterol) are formed by enzymatic reactions under physiological conditions [20].

27-hydroxycholesterol (27-OHC) is one of the most abundant oxysterols derived from the function of sterol 27-hydroxylase (CYP27A1) on cholesterol in the liver, where it becomes a substrate for bile acid (Fig. 3A). According to the tissue expression atlas, CYP27A1 transcripts and proteins are enriched in the liver and macrophages. When CYP27A1 was transfected into CHOP-C4 cells, 27-hydroxycholesterol levels were 2.5-fold higher than in control cells [8]. Conversely, loss-of-function in CYP27A1 analysis indicated that plasma concentrations of 27-OHC were significantly decreased [37]. Because oxysterol 7 alpha hydroxylase (CYP7B1) acts on the conversion of 27-OHC into bile acid, mice with *Cyp7b1* deletions showed increased levels of 27-OHC and decreased bile acids in plasma [36]. CYP7B1 expression is mainly limited to the liver and lungs, although it is also detected in the kidneys and brain [17]. Initially, identifying the function of 27-OHC in atherosclerosis progression started with the fact that the most abundant oxysterol in human atheromatous plaque was 27-OHC, and that the severity of atherosclerosis increased together with 27-OHC levels [9]. As expected, in-

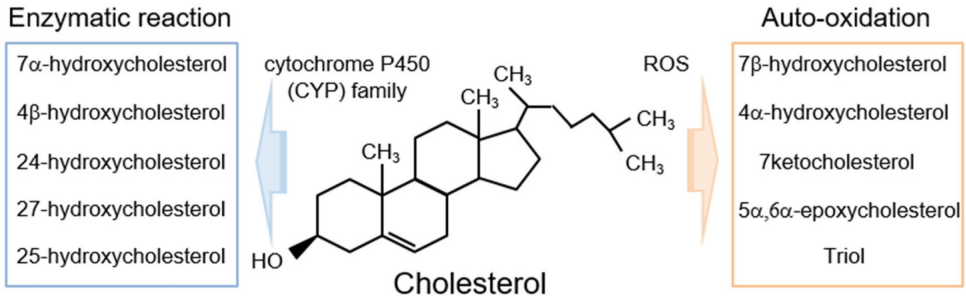

Fig. 2. Generation of common oxysterol from cholesterol. Enzymatic modification of cholesterol generates side chain oxidation to make 7α-hydroxycholesterol (7α-HC), 24-hydroxycholesterol (24-HC) and 27-hydroxycholesterol (27-HC). Non-enzymatic oxidation by reactive oxygen species forms 7β-hydroxycholesterol (7β-HC), 5α,6α-epoxycholesterol, and 7-ketocholesterol (7-KC).

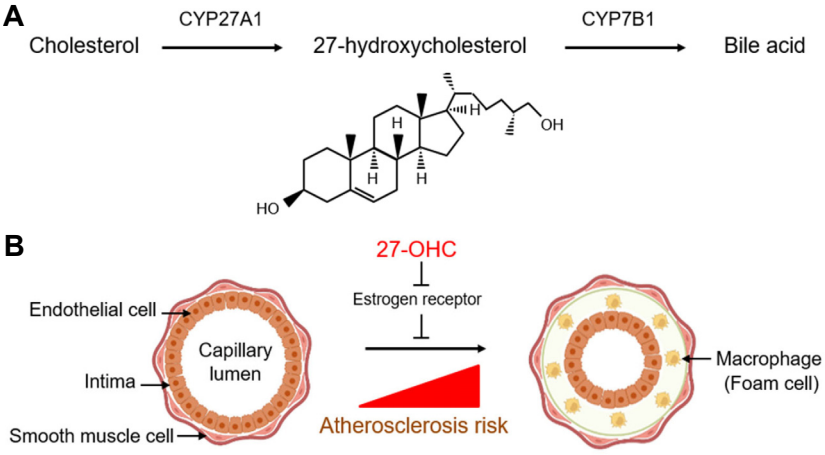

Fig. 3. 27-hydroxycholesterol increases atherosclerosis risk in an estrogen receptor-dependent manner. (A) Cholesterol 27-hydroxylase (CYP27A1) catalyzes conversion of cholesterol into 27-OHC, while oxysterol 7 alpha hydroxylase (CYP7B1) metabolizes 27-OHC. (B) In the vascular region, 27-OHC increases the infiltration of foam cells into intimal region, which contributes to the inflammatory response and atherosclerosis.

creased levels of 27-OHC in *Cyp7b1* deletion mice stimulated atherosclerotic lesions, and an initial study focused on the estrogen receptor to determine the mechanism by which 27-OHC increases atherosclerosis risk. Generally, estrogen lowers atherosclerotic plaque formation and protects the vasculature from ischemia [24]. Importantly, Umetani et al. proved that estrogen receptor activation was largely inhibited when estrogen was treated together with 27-OHC in vascular cells [35](Fig. 3B). This result is interesting because 27-OHC increases rather than suppresses estrogen receptor activity in breast cancer [23]. How 27-OHC exerts both agonist and antagonist activities toward the estrogen receptor is not yet clear.

27-OHC in Obesity

Plasma levels of 27-OHC are closely related to those of cholesterol. Because hypercholesterolemia is a common feature in obese patients, several studies have focused on exploring the potential effects of 27-OHC in metabolic tissues.

Adipose tissue

White adipose tissue (WAT) is one of the two types of adipose tissue found in mammals and is associated with visceral fat, where extra energy is stored. In addition to energy storage, adipose tissues modulate glucose and fatty acid metabolism by secreting various hormones and cytokines, known as adipokines [27]. Since adipocyte dysfunction is an important driving force in the development of insulin resistance, several studies related to the function of 27-OHC in adipose tissue have been performed. Shirouchi et al. described that 27-OHC suppresses intracellular TG accumulation and lipogenic gene expression during adipocyte differentiation in 3T3-L1 cells [32]. In addition, TO901317 (TO), a potent agonist of liver X receptor (LXR)α, significantly increased TG content, while 27-OHC co-treatment significantly reduced intracellular TG levels. It is not clear whether 27-OHC directly inhibits TO-induced LXRα activation. Similar results have been reported using *Cyp27a1*-deficient 3T3-L1 and genetic knockout mice. There was no significant difference in the weights of the fat deposits and whole body weights. However, clear increases in adipocyte differenti-

ation of stromal vascular fraction cells isolated from *Cyp27a1*$^{-/-}$ mice were observed. Thus, 27-OHC, an enzymatic product of CYP27A1, likely acts as a negative regulator of adipogenesis [15]. Although detailed mechanisms, for example, activation of certain signaling or transcription factors responsible for such anti-adipogenic properties, have not been proven, these results suggest that 27-OHC prevents or alleviates obesity. In contrast, another animal study suggested that 27-OHC promotes body weight gain and adiposity by directly affecting WATs [1]. Since 27-OHC receptors, such as ERs and LXRs, are expressed in adipose tissue, the researcher confirmed which transcription factor mediates the adipogenic effect of 27-OHC. As a result, 27-OHC treatment did not stimulate additional body weight gain in ER-deficient mice, whereas LXRa/b-null mice with 27-OHC still showed increased body weight gain compared to vehicle-treated mice. Thus, 27-OHC seems to suppress ERa activity in adipocytes, because adipose tissue ERa expression is inversely associated with adiposity [42] and ERa deletion mice result in obesity [18]. The reason for the discrepancy between the *in vitro* and *in vivo* results is not clear (Fig. 4A). To better understand the effect of 27-OHC on fat tissue and whole-body adiposity, adipose tissue-specific ERa knockout mice can be a useful genetic model for follow-up studies. Finally, it would be worthwhile to determine whether 27-OHC affects brown adipose tissue and white adipose tissue.

Liver

The liver is a central peripheral organ involved in controlling glucose and lipid homeostasis. For glucose regulation, the liver has various pathways, such as glycogenesis, glycogenolysis, glycolysis, and gluconeogenesis [26]. Non-alcoholic fatty liver disease (NAFLD) is caused by excess lipid accumulation in the liver due to non-alcoholic factors, such as a high-fat diet and a high-cholesterol diet [28]. To confirm whether 27-OHC can change the intracellular distribution of cholesterol and hepatic inflammation status, bone marrow transplantation from irradiated wild type and *Cyp27a1*$^{-/-}$ mice to LDLR knockout mice (*Ldlr*$^{-/-}$) was performed [2]. As a result, increased hepatic inflammation and liver damage in mice given bone marrow transplants from *the Cyp27a1*$^{-/-}$ group were observed. In contrast, 27-OHC injection decreased the number of macrophages, neutrophils, and T cells in the liver, demonstrating that 27-OHC has anti-inflammatory properties. Surprisingly, plasma cholesterol levels were also decreased in 27-OHC injected mice than in control mice on the high-fat, high-cholesterol (HFC) diet. In addition to plasma cholesterol levels, a recent study showed that 27-OHC inhibits SREBP-1 activation and hepatic lipid accumulation in mice [14]. Lenti-viral overexpression of CYP27A1 increases circulating 27-OHC concentration and ameliorates systemic lipid accumulation and insulin resistance. Similar to the *in vivo* results, 27-OHC treatment in primary hepatocytes suppressed mRNA expressions of FAS, ACC, and SCD1, which are involved in the regulation of *de novo* lipogenesis. Importantly, 27-OHC induced INSIG-2 expression promoted the binding of INSIG-2 to SREBP-1, which is the mechanism by which 27-OHC prevents SREBP-1 activation and lipogenic gene expression. Thus, these two studies indicate that 27-OHC can regulate hepatic lipid metabolism and inflammation, which contribute to the treatment of NAFLD (Fig. 4B).

Reciprocal Regulation: Intestine and Liver for 27-OHC

Cholesterol 7α-hydroxylase (CYP7A1) and 27-hydroxylase (CYP27A1) initiate classic and alternative pathways for bile acid synthesis, respectively. Notably, Wahlström et al. showed that the gut microbiota regulates the expression of

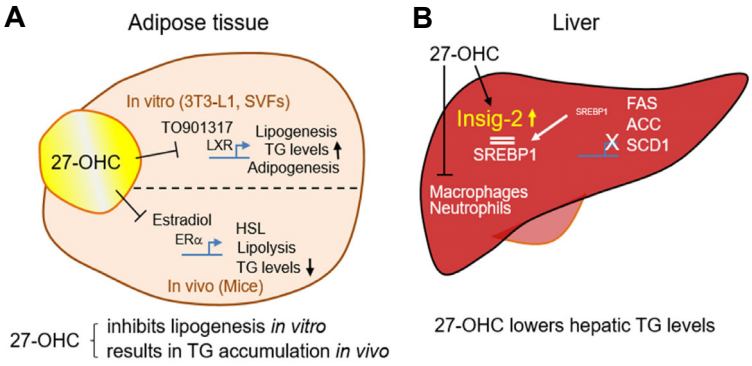

Fig. 4. Tissue-specific regulation of lipid metabolism by 27-hydroxycholesterol. (A) 27-OHC suppresses intracellular TG accumulation and adipogenesis in 3T3-L1 and stromal vascular fraction (SVF) cells (*Upper*). In contrast, subcutaneous injection of 27-OHC increases body weight and WAT mass in diet-induced obese mice in an ERa-dependent manner (*Lower*). (B) CYP27A1 overexpression increases plasma 27-OHC levels and alleviates hepatic steatosis. Also, 27-OHC inhibits lipid accumulation and inflammation in primary hepatocytes.

these enzymes [38]. Compared to control mice, germ-free mice showed significant increases in levels of bile acid synthetic enzymes in the liver. Similarly, apple polyphenol extract, which regulates gut microbiota composition, is characterized by increased relative abundance of *Akkermansia* and decreased relative abundance of *Lactobacillus*, which suppressed CYP27A1protein levels [13]. Taken together, these reports emphasize that gut microbiota can inhibit bile acid or intermediate levels, such as 27-OHC. Interestingly, 27-OHC treatment disrupted microbial composition and increased intestinal barrier permeability, which in turn decreased intestinal pathology [39]. Whether this effect contributes to colitis or systemic inflammation is not yet clear.

Conclusion and Future

As the estrogen receptor and LXR regulator, 27-OHC is involved in various pathophysiological conditions, including atherosclerosis, obesity, and brain disease. Because estrogen receptors are responsible for the anorexigenic effects of estrogen, confirming whether 27-OHC can modulate food intake or feeding behavior will be interesting for the metabolic research field. Recent studies have also shown that 27-OHC can induce macrophage gene expression through LXR-independent mechanisms, [12] or stimulate the STAT-3/VEGF pathway in an ER-independent manner [43]. Thus, the activation of different nuclear receptors or distinct signaling pathways induced by 27-OHC should be further investigated in the future. Finally, understanding how 27-OHC induces different effects between adipose tissue and the liver will provide important clues on the manner of developing 27-OHC as a new therapeutic target.

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The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

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초록 : 다양한 조직 및 질병에서 27-하이드록시콜레스테롤의 역할 및 기전 고찰

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옥시스테롤은 담즙산 합성 동안 일련의 효소 반응에 의해 생성된 콜레스테롤의 산화물로써, 콜레스테롤과 유사하게 세포내 영역으로 빠르게 이동하여 면역 세포 반응, 지질 대사 및 콜레스테롤 항상성과 같은 다양한 세포 과정을 조절한다. 글루코코르티코이드 수용체(GR), 에스트로겐 수용체(ER) 및 간 X 수용체(LXR)와 같은 종류의 핵 수용체는 여러 조직에서 옥시스테롤에 의해 조절될 수 있다. 가장 풍부한 옥시스테롤인 27-하이드록시콜레스테롤(27-OHC)은 조직 특이적 방식에 의해 에스트로겐 수용체 활성을 활성화하거나 억제하기 때문에 선택적 에스트로겐 수용체 조절자로 규명되었다. 특히 27-하이드록시콜레스테롤이 동맥 경화증 플라크에서 많이 발견되고 대식세포가 거품 세포로 변형되는 것을 가속화하기 때문에 동맥 경화증 발병에 기여하는 것이 분명해 보이나, 다른 연구들에서는 27-하이드록시콜레스테롤이 간 및 지방 조직을 포함한 다양한 대사 기관에 미치는 영향에 대해 반대 의견이 존재한다. 따라서 본 총설을 통해 대사 조직에서의 27-하이드록시콜레스테롤 역할에 대한 논의와 함께, 죽상 동맥 경화증 및 대사 증후군에 영향을 주는 27-하이드록시콜레스테롤의 세부 기전에 대해 논의하고자 한다.