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Review

# Fatty aldehyde and fatty alcohol metabolism: Review and importance for epidermal structure and function☆

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ABSTRACT

Normal fatty aldehyde and alcohol metabolism is essential for epidermal differentiation and function. Long-chain aldehydes are produced by catabolism of several lipids including fatty alcohols, sphingolipids, ether glycerolipids, isoprenoid alcohols and certain aliphatic lipids that undergo α- or ω-oxidation. The fatty aldehyde generated by these pathways is chiefly metabolized to fatty acid by fatty aldehyde dehydrogenase (FALDH, alternately known as ALDH3A2), which also functions to oxidize fatty alcohols as a component of the fatty alcohol:NAD oxidoreductase (FAO) enzyme complex. Genetic deficiency of FALDH/FAO in patients with Sjögren–Larsson syndrome (SLS) results in accumulation of fatty aldehydes, fatty alcohols and related lipids (ether glycerolipids, wax esters) in cultured keratinocytes. These biochemical changes are associated with abnormalities in formation of lamellar bodies in the stratum granulosum and impaired delivery of their precursor membranes to the stratum corneum (SC). The defective extracellular SC membranes are responsible for a leaky epidermal water barrier and ichthyosis. Although lamellar bodies appear to be the pathogenic target for abnormal fatty aldehyde/alcohol metabolism in SLS, the precise biochemical mechanisms are yet to be elucidated. Nevertheless, studies in SLS highlight the critical importance of FALDH and normal fatty aldehyde/alcohol metabolism for epidermal function. This article is part of a Special Issue entitled The Important Role of Lipids in the Epidermis and their Role in the Formation and Maintenance of the Cutaneous Barrier. Guest Editors: Kenneth R. Feingold and Peter Elias.

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## 1. Introduction

Medium- to long-chain aliphatic aldehydes and alcohols exist free in nature and are metabolic products of other precursor lipids. Fatty aldehydes and alcohols are structurally diverse and typically arise from metabolism of corresponding fatty acids. The aliphatic chains range from 6- to more than 26-carbons in length and are saturated, unsaturated or even methyl-branched. Most aldehydes and alcohols are used for biosynthesis of other lipids or are catabolic intermediates that are rapidly metabolized. Consequently, they are not essential components of cellular membranes and do not accumulate to a significant extent as free lipids. Because they comprise a very small proportion of the total lipid composition of mammalian tissues, they have been largely ignored and some of their most basic metabolic reactions are still poorly characterized.

Long-chain alcohols are known to be biosynthetic precursors for wax esters and ether glycerolipids. In contrast, lipophilic aldehydes have long been considered to have no essential physiologic role in mammals except for retinal, which is required for the visual cycle. More recent studies, however, have implicated some fatty aldehydes in thyroid function [1], cell proliferation [2] and as second messengers of oxidative stress [3].

Insight into the importance of fatty aldehyde and alcohol metabolism for epidermal biology is highlighted by the rare neurocutaneous disease Sjögren–Larsson syndrome (SLS). This disease is caused by genetic deficiency of fatty aldehyde dehydrogenase (FALDH) [4] and results in impaired oxidation of fatty aldehyde and fatty alcohol [5]. SLS patients have a defective epidermal water barrier and exhibit ichthyosis as a major symptom [6,7]. The study of SLS has uncovered the central role of FALDH in fatty aldehyde metabolism and provides a revealing glimpse into the functional consequences of deleterious aldehyde and alcohol metabolism for the epidermis.

Here, I review fatty aldehyde and alcohol metabolism as it relates to the skin and discuss the potential biochemical mechanisms responsible for epidermal dysfunction when FALDH is missing.

## 2. Aldehyde dehydrogenase and FALDH

Unlike fatty acids that are subject to a number of enzymatic modifications (desaturation, hydroxylation, oxidation, reduction, elongation,

*Abbreviations:* ALDH, aldehyde dehydrogenase; DHAP, dihydroxyacetone phosphate; ER, endoplasmic reticulum; FADH, fatty alcohol dehydrogenase; FALDH, fatty aldehyde dehydrogenase; FAO, fatty alcohol:NAD oxidoreductase; FAR, fatty acyl-CoA reductase; HMG-CoA, hydroxymethylglutaryl-CoA; 4-HNE, 4-hydroxynonenal; LB, lamellar body; PE, phosphatidylethanolamine; PKC, protein kinase C; PPARα, peroxisome proliferator activated receptor-α; ROS, reactive oxygen species; SC, stratum corneum; SG, stratum granulosum; SLS, Sjögren–Larsson syndrome; S1P, sphingosine-1-phosphate

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etc.), fatty aldehydes are largely limited to oxidation/reduction reactions. Few enzymes that metabolize fatty aldehydes have been studied directly in skin or in cultured keratinocytes. The most well characterized are aldehyde dehydrogenases (ALDHs), which catalyze the NAD(P)-dependent oxidation of aromatic and aliphatic aldehydes to their corresponding acids. The presence of several ALDHs in human skin has been demonstrated using histochemical and immunologic techniques with limited specificity for individual isozymes [8]. It is now known that humans possess a family of 19 ALDH genes encoding isozymes that vary in their tissue distribution, subcellular localization and substrate preferences [9]. These enzymes oxidize the many structurally diverse aldehydes produced by intermediary metabolism [10]. Most of the ALDHs do not have absolute substrate specificities and are capable of oxidizing structurally related aldehydes to varying degrees, which affords some level of metabolic redundancy. The repertoire of ALDH isozymes differs among tissues and the contribution of individual isozymes for specific aldehyde substrates may similarly vary. Using microarray and RNA-seq techniques, 11 of the ALDH genes are expressed in cultured human keratinocytes to an appreciable extent (unpublished observations). Of their corresponding ALDH isozymes, the most important one for epidermal function appears to be FALDH (also known as ALDH3A2), which acts on aliphatic aldehyde substrates [5]. At least two other ALDH isozymes (ALDH3A1 and ALDH3B1) have the capability to oxidize fatty aldehydes in vitro [11], but they are unable to compensate for FALDH deficiency and their singular importance for epidermal metabolism is not yet clear. In addition to ALDHs, some fatty aldehyde is metabolized to fatty alcohol by unidentified enzymes, most likely aldehyde reductase or by reversal of alcohol dehydrogenase.

FALDH catalyzes the $NAD^+$-dependent oxidation of long-chain aliphatic aldehydes to fatty acids [12–14]. The enzyme is capable of oxidizing a variety of aliphatic aldehydes ranging from 6- to at least 24-carbons long, including saturated, unsaturated and methyl-branched substrates, although retinal is not a substrate [12]. FALDH prefers long-chain substrates (C14–C18) over shorter ones, and the oxidative reaction is essentially irreversible. The enzyme has a subunit mass of 54 kDa and is catalytically active as a homodimer [15].

The gene for FALDH (*ALDH3A2*) consists of 11 exons and is located on chromosome 17p11.2. Alternative splicing of *ALDH3A2* results in two protein isoforms [16]. The major isoform is comprised of 485 amino acids and has a carboxy-terminal domain, which targets its localization to the endoplasmic reticulum (ER) where it encounters a variety of aldehyde substrates [17]. A minor protein isoform (FALDH*v*), which accounts for <10% of the total activity, is 508 amino acids long and differs from the major isoform by possessing a longer carboxy-terminal region. FALDH*v* is localized in peroxisomes, where it probably interacts with a more limited spectrum of aldehyde substrates [18]. In mouse, the relative expression of each isoform varies between tissues with greater expression of the FALDH*v* isoform in brain and testes [19].

FALDH is a housekeeping enzyme that is expressed in almost all cells and tissues. The enzyme is present throughout the epidermis in basal, spinous and granular keratinocytes, but is missing from the stratum corneum (SC) [20,21]. *ALDH3A2* is highly expressed in cultured keratinocytes and fibroblasts. The gene can be transcriptionally upregulated by certain pharmacologic agents and natural ligands that activate peroxisome proliferator activated receptor-α (PPARα), including fibrate drugs [22–24] and fatty acids such as linoleic acid [24], phytanic acid and pristanic acid [25]. This response is specifically mediated by a PPARα response element in the promoter of the gene [24]. The potential transcriptional role of other PPARs is unknown. *ALDH3A2* is also upregulated by insulin, and downregulated in an animal model of diabetes [26].

Owing to its broad substrate specificity, FALDH occupies a pivotal place in metabolism of aliphatic aldehydes generated by several diverse lipid pathways [27]. Deficiency of this enzyme results in accumulation of fatty aldehydes and certain aldehyde-related lipids, including fatty alcohols. It is therefore instructive to review the metabolism of fatty aldehyde and alcohol in the context of epidermal lipids.

## 3. Fatty aldehyde metabolism

Long-chain aliphatic aldehydes in mammals are largely produced by catabolic metabolism of several lipids, including ether glycerolipids, fatty alcohols, sphingolipids and wax esters (Fig. 1). Some medium-chain aliphatic aldehydes, such as hexanal, octanal and 4-hydroxy-2-nonenal (4-HNE), are produced via lipid peroxidation during oxidative stress. In addition, dietary sources of fatty aldehydes and aldehyde-generating lipids are an undefined and probably variable portion of the aldehyde metabolic pool in man.

### 3.1. Ether glycerolipid metabolism

Fatty aldehydes are generated through normal catabolism of ether glycerolipids [28] (Fig. 2). Most ether lipids in mammals are characterized by the presence of a long-chain alkyl group attached to the *sn* − 1 carbon of glycerol via an ether bond [29]. The alkyl chain is derived from fatty alcohols that are chiefly 16- to 18-carbons long. The enzyme that catalyzes formation of the ether-linked alkyl chain is alkyl-dihydroxyacetone phosphate-synthase (alkyl-DHAP-synthase), which is located in peroxisomes [30]. This unique reaction replaces the acyl group at the *sn* − 1 carbon of 1-acyl-DHAP with fatty alcohol, producing 1-*O*-alkyl-DHAP (Fig. 2). Subsequent enzymatic steps introduce a double bond into the alkyl chain at C1–C2 and culminate in the complete synthesis of plasmalogen forms of phospholipids (phosphatidylcholine, -ethanolamine and -serine) in which the *sn* − 1 position is occupied by a 1-*O*-alkenyl chain with an unsaturated vinyl ether bond (see Fig. 2 insert). Plasmalogens are present at high concentrations in erythrocytes and certain tissues (heart, brain, tumors), whereas neutral ether glycerolipids, such as 1-*O*-alkyl-2,3-diacyglycerol, are more abundant in skin. The neutral ether lipids in skin usually lack the double bond at the C1–C2 position of the *sn* − 1 alkyl chain and instead have a saturated or monounsaturated alkyl chain. These ether lipids are largely synthesized by sebaceous glands and secreted onto the surface of the skin as a component of sebum [31]. 1-*O*-Alkyl-2,3-diacyglycerol is also synthesized in cultured keratinocytes, suggesting a more widespread epidermal distribution [32,33].

The catabolism of ether glycerolipids involves enzymatic cleavage of the 1-*O*-alkyl bond by microsomal alkyl-glycerol monooxygenase [34] or lysoplasmalogenase [35], which releases the alkyl chain as fatty aldehyde. Studies on the degradation of 1-*O*-octadecyl-glycerol in SLS cultured fibroblasts and keratinocytes indicate that most of the fatty aldehyde produced is oxidized to fatty acid by FALDH, but a significant amount (up to 40%) is oxidized to fatty acid by another enzyme or reduced to fatty alcohol [36].

### 3.2. Fatty aldehydes produced by oxidative stress

Oxidative stress generates a spectrum of aldehydes that originate from the peroxidative cleavage of polyunsaturated fatty acids by reactive oxygen species (ROS) [37] (Fig. 3). These include short-chain aldehydes, such as malondialdehyde, and medium-chain aldehydes, including hexanal, octanal, nonenal and 2 hydroxy-alkenals.

4-Hydroxy-2-nonenal (4-HNE) is among the most reactive and toxic aldehydes generated by lipid peroxidation [38,37]. Its propensity to form covalent adducts with protein and lipid in cells is a sensitive measure of increased lipid peroxidation and oxidative stress [39]. In photodamaged skin, protein adducts of 4-HNE are increased as a result of oxidative stress [40]. Exposure of epidermal keratinocytes to ultraviolet-B light impairs detoxification of 4-HNE [41], which normally occurs by oxidation to its fatty acid or by conjugation with glutathione [42]. With its accumulation, 4-HNE itself may act as an agonist for

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