Prostaglandins, Leukotrienes and Essential Fatty Acids 88 (2013) 131–138

Contents lists available at SciVerse ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

journal homepage: www.elsevier.com/locate/plefa

Eicosanoids in skin inflammation

Anna Nicolaou *

School of Pharmacy and Centre for Skin Sciences, School of Life Sciences, University of Bradford, Richmond Road, Bradford BD7 1DP, UK

ARTICLE INFO

Keywords:
Skin
Eicosanoids
Polyunsaturated fatty acids
Inflammation

ABSTRACT

Eicosanoids play an integral part in homeostatic mechanisms related to skin health and structural integrity. They also mediate inflammatory events developed in response to environmental factors, such as exposure to ultraviolet radiation, and inflammatory and allergic disorders, including psoriasis and atopic dermatitis. This review article discusses biochemical aspects related to cutaneous eicosanoid metabolism, the contribution of these potent autacoids to skin inflammation and related conditions, and considers the importance of nutritional supplementation with bioactives such as omega-3 and omega-6 polyunsaturated fatty acids and plant-derived antioxidants as means of addressing skin health issues.

1. Introduction

Eicosanoids are produced by all cutaneous cell types and contribute to homeostatic processes and inflammatory responses associated with injury, allergy and other acute or chronic conditions [1–3]. Membrane phospholipid-esterified arachidonic acid (AA; 20:4n-6) and the C20 polyunsaturated fatty acids (PUFA) dihomo-gamma-linolenic acid (DGLA; 20:3n-6) and eicosapentaenoic acid (EPA; 20:5n-3) are mobilized by phospholipases and serve as precursors to various eicosanoids that are formed by cutaneous cyclooxygenase (COX) and terminal prostanoid synthases (PGS), lipoxygenase (LOX) and cytochrome P450 (CYP) enzymes. Eicosanoid-like molecules are also produced through non-enzymatic oxidations, whilst other n-6 and n-3 PUFA including linoleic acid (LA; 18:2n-6) and docosahexaenoic acid (DHA; 22:6n-3) can give rise to analogous lipid mediators [4,5] (Fig. 1).

Skin is considered the largest organs of the body and constitutes a physical barrier protecting it from injury, infection, water and electrolyte loss, as well as being an important player of the immune system [6]. It has a multilayered structure that supports the formation of a highly keratinized outer epidermal permeability barrier, whilst the epidermis and dermis host a number of primary cells including epidermal keratinocytes, melanocytes, and Langerhans cells, as well as dermal fibroblasts, mast cells, and infiltrating leukocytes. Inflammation partakes in physiological mechanisms mediating skin healing and repair post injury, whilst it is a central feature in a number of dermatoses and underpins cancer development. Skin cells participating in these events produce eicosanoids in response to various stimuli and this can be influenced by dietary manipulation; therefore an in depth appreciation of these potent lipid mediators of cutaneous inflammation is of great importance.

This article aims to review our current understanding of cutaneous eicosanoid production and their contribution to inflammatory conditions, and will discuss systemic and local interventions that have been considered as means of manipulating lipid mediator production with a view to improve skin health and develop chemopreventive regimes.

2. Cutaneous eicosanoid biology

Fatty acids are crucial for skin structure and function, as shown by the seminal studies of Burr and Burr [7] that demonstrated its dependence on systemically provided essential fatty acids. LA constitutes approximately 12% of cutaneous fatty acids and is pivotal for the integrity of the epidermal barrier [8–10]. Furthermore, epidermal keratinocytes are characterized by lack of Δ5 and Δ6 desaturase activity [11] and rely on systemic provision of long chain PUFA such as AA, DHA and EPA that, collectively, account for no more than 5% of total fatty acids [12]. Although their precursors are found at such low levels, PUFA-derived prostanoids and hydroxy-fatty acids are important for skin physiology and homeostasis [9,13,14].

2.1. Phospholipases

Phospholipase A_2 (PLA_2) is the principle lipolytic enzyme providing AA and other PUFA for eicosanoid biosynthesis [15]. Of the many isoforms, the cytosolic PLA_2 ($cPLA_2$) is considered the main enzyme mediating the release of AA for cutaneous eicosanoids with its activity and expression found induced in conditions

* Tel.: +44 1274 234717; fax: +44 1274 235600.
E-mail address: a.nicolaou@bradford.ac.uk

0952-3278/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.plefa.2012.03.009

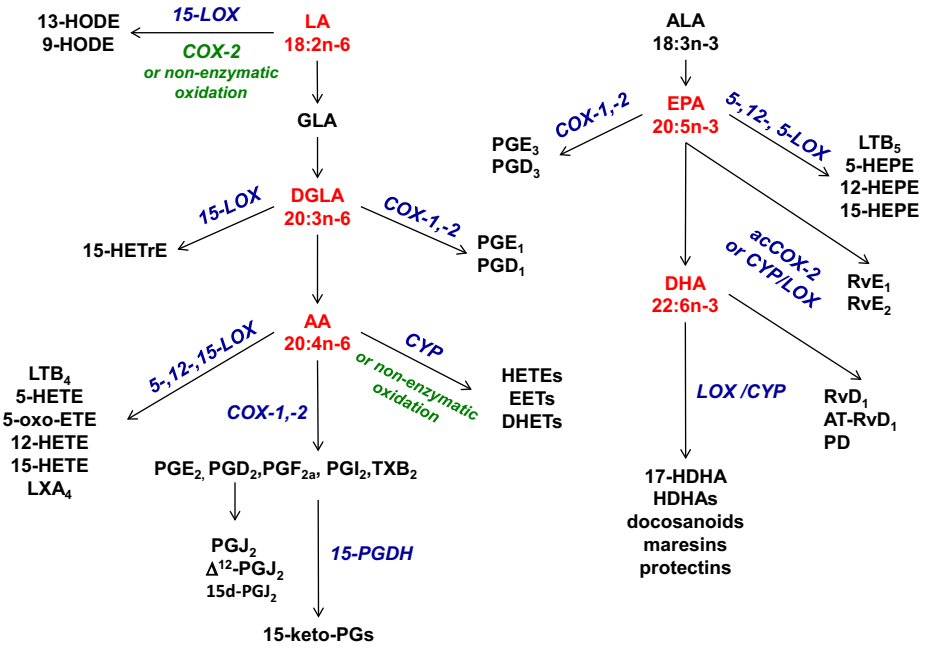

Fig. 1. Schematic overview of biosynthetic pathways for the main biologically relevant oxygenated products of polyunsaturated fatty acids. acCOX: acetylated COX; AT-RvD$_1$: aspirin triggered RvD$_1$.

Table 1
Biological effects of selective eicosanoids involved in cutaneous inflammation.

Metabolite	Biological effect	Cellular origin
PGE_2	Vasodilatation; immunosuppression; chemotaxis; proliferation; pigmentation	Epidermal keratinocytes; dermal fibroblasts
PGD_2	Immunomodulation	Langerhans cells; mast cells; epidermal keratinocytes
12*S*-HETE	Chemotaxis—leukocyte migration; proliferation	Epidermal keratinocytes; Langerhans cells; dermal fibroblasts
15*S*-HETE	Anti-inflammatory; counteracts 12*S*-HETE and LTB_4 effects	Epidermal keratinocytes; dermal fibroblasts
13*S*-HODE	Anti-inflammatory; anti-proliferatory	Epidermal keratinocytes; dermal fibroblasts
15*S*-HETrE	Anti-inflammatory	Epidermal keratinocytes; dermal fibroblasts
LTB_4	Chemotaxis	Infiltrating leukocytes; epidermal keratinocytes (low levels)

characterized by oxidative stress (e.g. sunburn) [16]. The secretory PLA_2 (sPLA2) has also been found in keratinocytes and sites of cutaneous inflammation (e.g. psoriasis) [17,18]. Finally, phosphatidylinositol (PI)-specific phospholipase C (PLC) that releases diacylglycerol (DAG) which can be further metabolized by lipases to generate AA and in this way potentially contribute to skin eicosanoids, has also been reported to be involved in certain inflammatory conditions (e.g. psoriasis) [19,20].

2.2. Cyclooxygenase-derived mediators

Cyclooxygenase isoforms, i.e. the constitutive COX-1 and inducible COX-2, convert AA to the unstable intermediate PGH_2 that is further isomerized to prostaglandins, prostacylin or thromboxanes (prostanoids) depending on the prevalence of the corresponding terminal prostanoid syntases. EPA and DGLA are also metabolized by COX and generate a range of prostanoids (Fig. 1). Most mammalian cutaneous cells express COX-1 and -2, and studies on human and animal skin have shown the production of PGE_2, PGE_1, PGE_3, PGD_2, $PGF_{2\alpha}$, PGI_2, and TXB_2 [13,21,22]. However, the exact prostanoid profile for each skin cell type, and the influence these mediators may have on transcellular metabolism and the overall skin function continues to be of interest (Table 1).

PGE_2 is one of the main cutaneous eicosanoids produced by both epidermal keratinocytes and dermal fibroblasts. It exhibits potent pro-inflammatory and vasodilatory properties, promotes proliferation and modulates immunosuppression [22,23]. These effects are mediated through G-protein coupled receptors EP1-4 expressed in all primary skin cells [24–27]. PGE_2 is formed via the cytosolic and microsomal PGE synthases (cPGES, mPGES-1 and mPGES-2) [28]. Interestingly, there is evident for linked expression of the inducible mPGES-1 and COX-2 isozymes demonstrating in skin cells the presence of an efficient system for increased PGE_2 production upon stimulation [29]. Furthermore, PGE_2 is involved in keratinocyte proliferation and differentiation, and this has direct consequences for the epidermal barrier function [25,30,31]. It has also been suggested that fibroblast-produced PGE_2 influences keratinocyte growth showing the cross-talk and biochemical support between skin layers [32,33]. Finally, PGE_2 can act as keratinocyte chemoattractant and modulator of dermal fibroblasts, and in this way can facilitate wound healing [34,35]. Recent reports suggest that epidermal melanocytes can also produce PGE_2 although the lack of COX-2 protein expression in these cells may explain the relatively low levels observed [36,37]. However, PGE_2 has a direct effect on melanocyte-mediated post-inflammatory pigmentary responses and melanocyte dendricity showing relevance to skin tanning [27,38].

Langerhans cells and dermal mast cells are considered to be the principle producers of cutaneous PGD_2, a potent anti-proliferative and anti-inflammatory prostaglandin involved in immune and allergic responses [23,39]. It exhibits its effects through the CRTH2 and DP receptors expressed in various skin cells, including keratinocytes [40,41]. Recent studies have shown the production of PGD_2 by epidermal melanocytes [37]. Notably, Langerhans cells