Metabolism of polyunsaturated fatty acids by skin epidermal enzymes: generation of antiinflammatory and antiproliferative metabolites[1–3]

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ABSTRACT In the skin epidermis, the metabolism of polyunsaturated fatty acids (PUFAs) is highly active. Dietary deficiency of linoleic acid (LA), the major 18-carbon n−6 PUFA in normal epidermis, results in a characteristic scaly skin disorder and excessive epidermal water loss. Because of the inability of normal skin epidermis to desaturate LA to γ-linolenic acid, it is transformed by epidermal 15-lipoxygenase to mainly 13-hydroxyoctadecadienoic acid, which functionally exerts antiproliferative properties in the tissue. In contrast, compared with LA, arachidonic acid (AA) is a relatively minor 20-carbon n−6 PUFA in the skin and is metabolized via the cyclooxygenase pathway, predominantly to the prostaglandins E_2, $F_{2\alpha}$, and D_2. AA is also metabolized via the 15-lipoxygenase pathway, predominantly to 15-hydroxyeicosatetraenoic acid. At low concentrations, the prostaglandins function to modulate normal skin physiologic processes, whereas at high concentrations they induce inflammatory processes. PUFAs derived from other dietary oils are also transformed mainly into monohydroxy fatty acids. For instance, epidermal 15-lipoxygenase transforms dihomo-γ-linolenic acid (20:3n−6) to 15-hydroxyeicosatrienoic acid, eicosapentaenoic acid (20:5n−3) to 15-hydroxyeicosapentaenoic acid, and docosahexaenoic acid (22:6n−3) to 17-hydroxydocosahexaenoic acid, respectively. These monohydroxy acids exhibit antiinflammatory properties in vitro. Thus, supplementation of diets with appropriate purified vegetable oils, fish oil, or both may generate local cutaneous antiinflammatory and antiproliferative metabolites which could serve as less toxic in vivo monotherapies or as adjuncts to standard therapeutic regimens for the management of inflammatory skin disorders. *Am J Clin Nutr* 2000;71(suppl):361S–6S.

KEY WORDS Arachidonic acid, dihomo-γ-linolenic acid, DGLA, docosahexaenoic acid, DHA, essential fatty acid, eicosapentaenoic acid, EPA, γ-linolenic acid, GLA, 13-hydroxyoctadecadienoic acid, 13-HODE, 13-HODE-substituted diacylglycerol, leukotriene B_4, LTB_4, prostaglandin E_2, PGE_2, protein kinase C, polymorphonuclear cell, polyunsaturated fatty acid, PUFA

INTRODUCTION

The first indication that dietary fat might be essential for healthy, growing animals was presented in 1918 by Aron (1), who proposed that butter has a nutrient value that cannot be provided by other dietary components. This report suggested that there was a special nutritive value inherent in fat apart from its caloric contribution and that this might be related to the presence of certain lipids. In 1929, Burr and Burr (2) published the first in a series of papers outlining a "new deficiency disease produced by the rigid exclusion of fat from the diet." They developed the hypothesis that warm-blooded animals in general cannot synthesize appreciable quantities of certain fatty acids. In 1930, these investigators added significantly to their earlier work by presenting evidence that the consumption of linoleic acid (LA; 18:2n−6) alone could reverse all deficiency symptoms resulting from a fat-free diet and thus LA was heralded as an essential fatty acid (EFA; 3). This pioneering study also indicated that, in addition to the visible scaliness of the skin, animals with EFA deficiency experienced increased water loss through the skin. Thus, Burr and Burr recognized in these early studies the 2 major defects that have been associated with EFA deficiency in cutaneous biology, namely epidermal hyperproliferation and increased permeability of the skin to water.

BIOLOGICAL SIGNIFICANCE OF 18-CARBON POLYUNSATURATED FATTY ACIDS IN THE EPIDERMIS

Linoleic acid and 13-hydroxyoctadecadienoic acid

Role in skin water barrier system

The most abundant polyunsaturated fatty acid (PUFA) in human skin is the 18-carbon fatty acid, LA (4). There is good evidence indicating that one functional role of LA is its involvement in the maintenance of the epidermal water barrier (5); disruption of this barrier is one of the major abnormalities in cutaneous EFA deficiency. The physical structure of the epidermal water barrier has been ascribed to sheets of stacked lipid bilayers, or lamellae, which fill the intercellular spaces of the uppermost layer of the epidermis (stratum corneum). These lipid bilayers contain large amounts of sphingolipids (6), of which the

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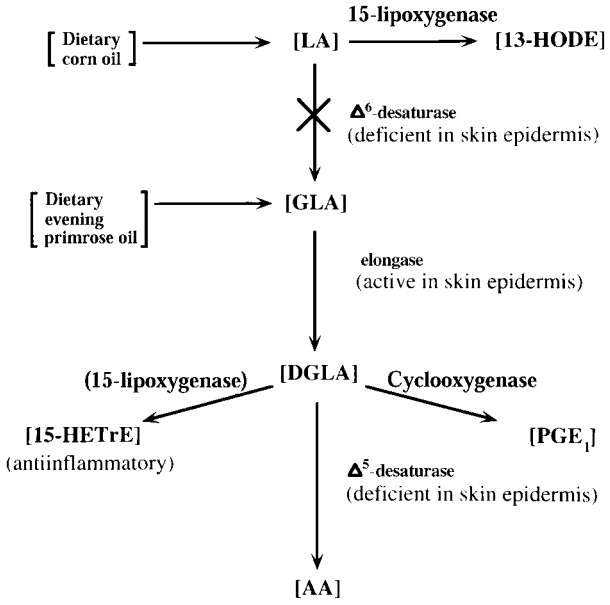

FIGURE 1. Metabolism of dietary linoleic acid (LA) and γ-linolenic acid (GLA) in skin epidermis. 13-HODE, 13-hydroxyoctadecadienoic acid; DGLA, dihomo-γ-linolenic acid; 15-HETrE, 15-hydroxyeicosatrienoic acid; PGE_1, prostaglandin E_1; AA, arachidonic acid.

linoleate-rich species have been characterized as acylglucosylceramide, acylceramide, and a unique acylacid (7–9). It has been suggested that the linoleyl moiety of the barrier acylsphingolipids is further metabolized by a lipoxygenase-like reaction to form first a hydroxyacylceramide and then a polyoxyacylceramide before the barrier function is exhibited (10).

Generation of 13-hydroxyoctadecadienoic acid by 15-lipoxygenase: role in epidermal hyperproliferation

Although the feeding of LA to EFA-deficient animals is known to reverse the major cutaneous symptoms of EFA deficiency (which include hyperproliferation and increased transepidermal water loss), the mechanism for such a reversal has remained unknown. As a first step towards elucidating the reversal of hyperproliferative scaly skin lesions by dietary LA, we incubated LA with soybean 15-lipoxygenase (EC 1.13.11.33) or 15-lipoxygenase prepared from skin epidermis. The major metabolite identified in these incubations was 13-hydroxyoctadecadienoic acid (13-HODE) and a minor metabolite was 9-HODE. The skin epidermis is unique in that it preferentially metabolizes LA to 13-HODE with a negligible amount transformed to γ-linolenic acid (GLA), suggesting that this metabolite may play a role in vivo. Similarly, the feeding of corn oil to normal guinea pigs led to enhanced amounts of 13-HODE in the skin epidermis. A schematic illustration of the metabolism of dietary LA and GLA in the epidermis is shown in **Figure 1**. In attempts to identify a mode of action, subsequent studies revealed that 13-HODE was incorporated into epidermal phosphatidylinositol 4,5-bisphosphate, resulting in epidermal phospholipase C–catalyzed release of 13-HODE into a novel 13-HODE-containing diacylglycerol (1-acyl-2–13-HODE-glycerol) (11). The possibility now exists that this novel 13-HODE-containing diacylglycerol could function to modulate the activity of epidermal protein kinase C (PKC) and epidermal hyperproliferation and differentiation.

Modulation of cellular signaling by 13-HODE–substituted diacylglycerol

To determine whether or not 13-HODE–substituted diacylglycerol can modulate cellular signaling, we biosynthesized 1-palmitoyl-2–13-HODE–substituted diacylglycerol from 13-HODE–containing phosphatidylcholine. Treatment with phospholipase C released a novel 1-palmitoyl-2–13-HODE–substituted diacylglycerol (11). We determined the effects of the putative 13-HODE–substituted diacylglycerol on total epidermal PKC activity and expression of 2 epidermal PKC isozymes, PKC-β and PKC-α. The resulting data revealed marked inhibition of total PKC activity with substantial selectivity for inhibition of PKC-β but a negligible effect on PKC-α (12). Thus, 13-HODE–substituted diacylglycerol had a selective inhibitory effect on the activity of a major epidermal PKC isozyme. These results suggest that 13-HODE–containing diacylglycerol can modulate epidermal PKC activity and expression, which are purportedly associated with epidermal hyperproliferation.

Possible in vivo regulatory role of 13-HODE–substituted diacylglycerol

To ascertain the in vivo relevance of 13-HODE–substituted diacylglycerol, we determined whether 13-HODE and 13-HODE–substituted diacylglycerol accumulate in the skin epidermis of guinea pigs after feeding with safflower oil containing LA. To accomplish this, guinea pigs were made EFA-deficient by feeding them a basal diet supplemented with 4% hydrogenated coconut oil for 8 wk. Tissue concentrations of putative 13-HODE–substituted diacylglycerol and PKC isozymes, tissue hyperproliferation (determined by ^{3}H-thymidine uptake), and histologic evaluations were determined in epidermal preparations from guinea pigs fed *1*) safflower oil (controls), *2*) only the EFA-deficient diet, and *3*) the EFA-deficient diet followed by safflower oil for 2 wk (reversed guinea pigs). Our findings revealed that cutaneous 13-HODE and 13-HODE–substituted diacylglycerol were significantly lower in EFA-deficient animals than in normal safflower-oil–fed animals. The 13-HODE and 13-HODE–substituted diacylglycerol reductions paralleled both epidermal hyperproliferation (scaly lesions) and elevated expression and activities of PKC-α and -β in the EFA-deficient animals. Refeeding the animals with safflower oil for 2 wk replenished tissue concentrations of 13-HODE and 13-HODE–substituted diacylglycerol, which inversely correlated with the selective down-regulation of PKC-β expression as well as suppression of epidermal hyperproliferation. In contrast, the expression and activity of PKC-α were elevated in the epidermis of the EFA-deficient guinea pigs, but were not down-regulated after refeeding with the safflower-oil diet (13). A summary of data derived from these studies is shown in **Figure 2**. These results suggest that the epidermal concentration of 13-HODE, which is derived from dietary LA, plays a role in vivo in modulating cutaneous hyperproliferation via the generation of 13-HODE–substituted diacylglycerol and its selective suppression of PKC-β. A speculative scenario describing the association of dietary LA-enriched oil with elevation of 13-HODE in the tissue, the generation of putative 13-HODE–substituted diacylglycerol, and its down-regulation of PKC-β is illustrated in **Figure 3**.

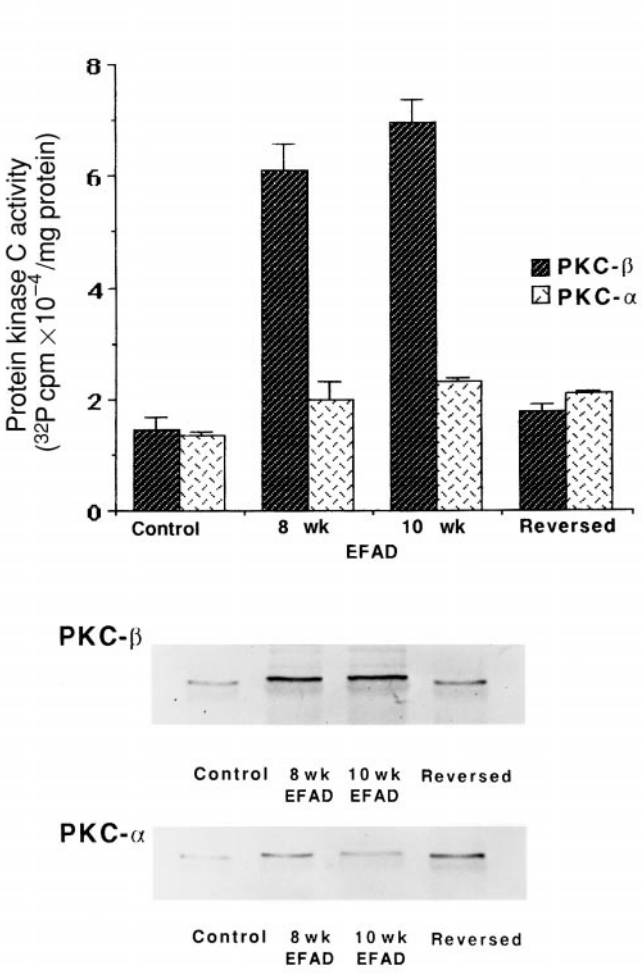

FIGURE 2. Essential fatty acid deficiency–induced epidermal hyperproliferation and protein kinase C (PKC)-β activity are suppressed by dietary linoleic acid. Membrane-associated epidermal PKC isozyme (β and α) activities were determined in the epidermal extracts from control, essential fatty acid–deficient (EFAD), and reversed guinea pigs (EFAD animals restored to normal). Specifically, epidermal high-speed particulate membrane fractions were prepared, and PKC isozyme activities from each dietary group were assayed as described previously (12). The upper portion of the figure represents PKC-β and PKC-α activities of the 3 dietary groups of animals; values are means ± SD (n = 12) from 3 separate experiments. The lower portion of the figure represents the expression of the 2 PKC isozymes. To determine PKC-β and PKC-α expressions, 30 mg protein of solubilized epidermal membrane preparation from each dietary group was subjected to gel electrophoresis [sodium dodecyl sulfate-polyacylamide gel electrophoresis, 10% gel] followed by Western blot assay with specific PKC-α and PKC-β antibodies as described previously (12). The gel electrophoresis data were reproducible in 3 separate experiments. Adapted from reference 13.

BIOLOGICAL SIGNIFICANCE OF 20-CARBON PUFAS IN THE EPIDERMIS

Arachidonic acid

The 20-carbon fatty acid arachidonic acid (AA; 20:4n−6) is the second most prominent PUFA in the skin. AA makes up ≈6–10% of the total fatty acids in the epidermal phospholipids of guinea pigs and ≈9% in human skin (14). The functional role of AA depends largely on its generation of biologically potent oxidative metabolites, namely prostaglandins and hydroxy fatty acids. When released after catalytic hydrolysis by epidermal cytosolic phospholipase A_2, AA undergoes oxidative transformations via the cyclooxgenase pathway and generates prostaglandin E_2 (PGE_2), $PGF_{2\alpha}$, and PGD_2. The major lipoxygenase pathway enzyme in the epidermis is epidermal 15-lipoxygenase, which catalyzes the generation of 15-hydroxyeicosatetraenoic acid (15-HETE) from AA. Interestingly, leukotriene-A_4 hydrolase (EC 3.3.26), the enzyme that transforms leukotriene A_4 (LTA_4) to LTB_4, has also been identified in the epidermis and presumably functions to transform polymorphonuclear-cell–derived LTA_4 into LTB_4 (15), a proinflammatory metabolite. This latter possibility explains, at least in part, the elevated LTB_4 concentrations in leukocyte-infiltrated cutaneous inflammatory reactions in psoriasis. The amount of 5-lipoxygenase in the epidermis is negligible and thus this enzyme does not appreciably transform AA to LTB_4. Therefore, a major lipoxygenase metabolite from AA in the epidermis is 15-HETE.

Dihomo-γ-linolenic acid

Dihomo-γ-linolenic acid (DGLA; 20:3n−6), although a small constituent of normal epidermis, is formed as an elongation product of dietary γ-linolenic acid (GLA; 18:3n−6). When its concentration is elevated in the tissue, it is metabolized by epidermal cyclooxygenase to prostaglandin of the 1-series (PGE_1) and also by 15-lipoxygenase to 15-hydroxyeicosatrienoic acid (15-HETrE). Human epidermis and guinea pig epidermis both contain an active elongase enzyme that converts the dietary precursor GLA to DGLA (16). For instance, supplementation of human (17) or guinea pig (18) diets with evening primrose or borage oil (vegetable oils that contain GLA) raises epidermal PGE_1 and 15-HETrE concentrations. Interestingly, as shown in Figure 1, Δ^5-desaturase enzyme is deficient in the epidermis and thus dietary GLA is not metabolized in significant amounts to AA. Because evening primrose oil has been used in the clinical management of inflammatory hyperproliferative disorders of the skin (19, 20), its reported beneficial effects may be due, at least in part, to epidermal generation of PGE_1 and 15-HETrE from elevated tissue DGLA concentrations.

Eicosapentaenoic acid and docosahexaenoic acid

Eicosapentaenoic acid (EPA; 20:5n−3) and docosahexaenoic acid (DHA; 22:6n−3) are the 2 major PUFAs derived from fish oils. They are not present in normal epidermis. Although α-linolenic acid (18:3n−3) and its oxidative metabolites, EPA and DHA, are absent in normal epidermis, both EPA and DHA are metabolized by skin epidermal 15-lipoxygenase to predominantly monohydroxylated metabolites: 15-hydroxyeicosapentaenoic acid (15-HEPE) and 17-hydroxydocosahexaenoic acid (17-HoDHE), respectively. Interestingly, it was reported that these metabolites accumulated in the epidermis after ingestion of fish oils (21, 22). This possibility may explain, at least in part, the beneficial effects of dietary fish oil on cutaneous inflammation.

Attenuation of the proinflammatory mediator LTB_4 generated from arachidonic acid by dietary PUFAs

To evaluate whether these 20-carbon monohydroxy fatty acids exert effects on inflammatory processes, we tested the in vitro

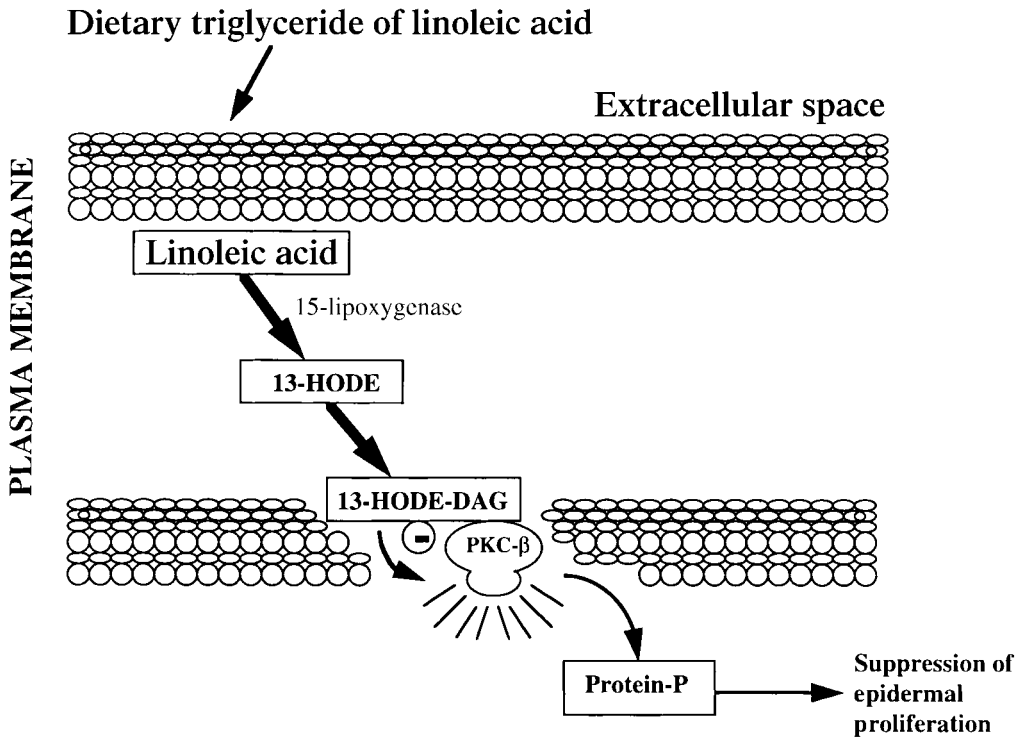

FIGURE 3. A speculative scenario showing how dietary linoleic acid could suppress skin hyperproliferation via cutaneous generation of putative 13-hydroxyoctadecadienoic acid (13-HODE)–substituted diacylglycerol (13-HODE-DAG). PKC-β, protein kinase C-β; protein-P, phosphorylated protein.

effects of 15-HETE (derived from AA), 15-HETrE (derived from DGLA), 15-HEPE (derived from EPA) and 17-HoDHE (derived from DHA) on the biosynthesis of polymorphonuclear-cell–derived proinflammatory LTB_4 (22). The data shown in **Figure 4** revealed that 15-HETrE derived from dietary GLA was most potent at lower concentrations.

DISCUSSION

Because the precursors of eicosanoids are derived from dietary PUFAs, it is reasonable to speculate that the in vivo synthesis of the proinflammatory mediators generated from AA can be modulated by manipulation of dietary PUFAs. For instance, supplementing the diets of patients with psoriasis (an inflammatory proliferative skin disorder) with fish oil containing the n−3 PUFAs EPA and DHA has been reported to alleviate the lesions with moderate-to-excellent results (23–27). This approach provides an alternative or adjunct protocol for the management of psoriasis with negligible side effects. The reported efficacy of these dietary PUFAs is compatible with the in vitro results showing that diets supplemented with EPA- and DHA-containing oils can alter the profile of endogenous epidermal phospholipid fatty acids by elevating the concentrations of EPA and DHA in epidermal phospholipids. After the hydrolytic release of the PUFAs from phospholipids, they are metabolized by epidermal 15-lipoxygenase to 15-HEPE and 17-HoDHE, which attenuate the biosynthesis of the proinflammatory eicosanoids from infiltrating polymorphonuclear cells.

Additionally, although the 18-carbon 13-HODE derived from LA exerts moderate antiinflammatory effects in vitro, it exerts potent antiproliferative effects in vivo, as evidenced by the reduction of epidermal scaly lesions (13). Overall, these findings underscore the significance of 15-lipoxygenase monohydroxylated metabolites generated from PUFAs in the skin, indicating that they may play important roles in vivo. These metabolites may, in concert with other cellular processes, attenuate inflam-

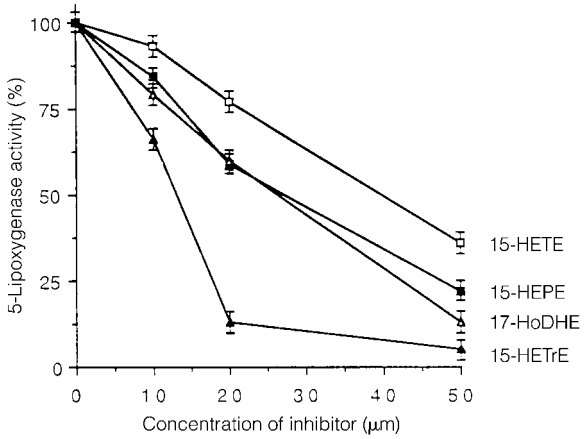

FIGURE 4. Inhibition of RBL-1 leukemia cells' 5-lipoxygenase–catalyzed transformation of arachidonic acid to leukotriene B_4 by the monohydroxy fatty acids 15-hydroxyeicosatetraenoic acid (15-HETE), 15-hydroxyeicosapentaenoic acid (15-HEPE), 17-hydroxydocosahexaenoic acid, (17-HoDHE), and 15-hydroxyeicosatrienoic acid (15-HETrE). The inhibitory effects of these monohydroxy fatty acids were ascertained by incubation with RBL-1 cell homogenates. Each point represents the mean ± SEM of triplicate determinations from 3 separate experiments. From reference 22.

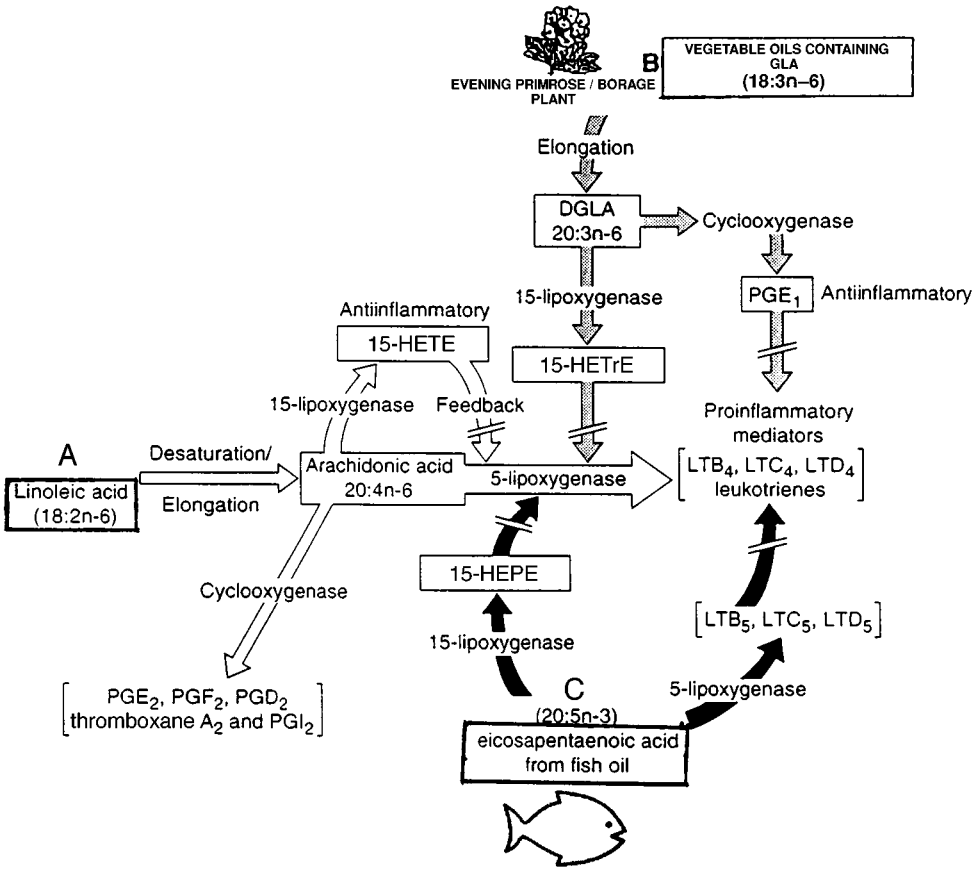

FIGURE 5. A speculative scenario of the possible attenuating effects of the constituent polyunsaturated fatty acids and metabolites from vegetable and fish oils on the generation of proinflammatory leukotrienes from arachidonic acid (AA). The A pathway illustrates the metabolic transformations from dietary intake of safflower oil, which is rich in linoleic acid (LA). It shows the in vivo desaturation and elongation of LA to AA followed by 5-lipoxygenation of AA to proinflammatory leukotrienes (LTs) (particularly LTB_4) by polymorphonuclear cells. AA is also metabolized by 15-lipoxygenase to 15-hydroxyeicosatetraenoic acid (15-HETE), which exerts antiinflammatory activity in the skin (28). The B pathway illustrates the epidermal elongation of dietary γ-linolenic acid (GLA), a constituent of evening primrose and borage oils, to dihomo-γ-linolenic acid (DGLA), followed by 15-lipoxygenation of DGLA to 15-hydroxyeicosatrienoic acid (15-HETrE) and cyclooxygenation to prostaglandin E_1 (PGE_1). The C pathway illustrates the 15-lipoxygenation of dietary eicosapentaenoic acid to 15-hydroxyeicosapentaenoic acid (15-HEPE) and the 5-lipoxygenation to LTB_5.

matory and proliferative cutaneous disorders. In **Figure 5**, a speculative scenario of the possible modulatory effects of the constituent PUFAs and their 15-lipoxygenase metabolites from vegetable and fish oils on the generation of pro-inflammatory leukotrienes from AA is shown.

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