Essential Fatty Acids/Eicosanoid Biosynthesis in the Skin: Biological Significance (43670)

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The first indication that dietary fat may be essential for healthy growing animals was presented in 1918 by Aron, who proposed that butter has a nutrient value that cannot be provided by other dietary components (1). This report suggested that there was a special nutritive value inherent in fat apart from its caloric contribution and that this possibly was related to the presence of certain lipids. In 1929, Burr and Burr (2) presented 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, both investigators significantly added to their earlier work by presenting evidence that the dietary inclusion of linoleic acid alone could reverse all deficiency symptoms resulting from a fat-free diet and thus linoleic acid (LA or 18:2n-6[2]) was heralded as an "essential fatty acid" (EFA) (3). This pioneering study contained additional observations which indicated that besides the visible scaliness of the skin, animals with essential fatty acid deficiency (EFA-deficiency) also experience increased water consumption without increased urine output leading to speculation of increased water loss through the skin. Thus, Burr recognized in these early studies the two major defects that have been associated with EFA deficiency in cutaneous biology, namely: epidermal hyperproliferation and an increased permeability of the skin to water.

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[2] Fatty acids and acyl groups are denoted 18:2n-6, 18:3n-3 and so on, with the first number representing the number of carbons in the acyl chain, the number following the colon indicating the number of methylene interrupted cis-double bonds and the number of "n" (or "w") indicating the number of carbon atoms from the methyl end of the acyl chain to the nearest double bond.

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Structural Forms

Three major families of unsaturated fatty acids (UFAs) are characteristic of mammalian species: the n-9, the n-6, and the n-3 UFAs. The n-6 and n-3 polyunsaturated fatty acids (PUFAs) are defined by the position of the double bond closest to the terminal methyl group of the fatty acid molecule. For instance, in the n-6 family, the first double bond occurs between the sixth and seventh carbons from the methyl group end of the molecule, whereas in the n-3 family the first double bond occurs between the third and fourth carbons. These structural forms are shown in Figure 1. These basic structures cannot be synthesized *de novo* by vertebrate animals nor are the n-3 and n-6 families of PUFAs interconvertible. Thus, these PUFAs must be obtained from diet.

Biochemistry of EFA

Dietary Sources. The 18-carbon n-6 and n-3 polyunsaturated fatty acids (PUFAs) are synthesized on land by many plants and therefore are obtained from vegetable oils. However, the longer chain members of each family are either biosynthesized in vivo after dietary ingestion of the shorter 18-carbon precursors or they are obtained directly from animal or marine sources. For example, the longer chain n-3 PUFAs, eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), are found in fish and marine oils and therefore can be ingested directly from these sources. The important longer chain n-6 PUFA, arachidonic acid (AA, 20:4n-6), is found in liver, brain, and muscle, which are rich dietary sources of arachidonic acid.

Metabolism of EFA

Generalized Desaturation and Elongation of Shorter Chain PUFAs. The shorter chain EFA's, linoleic acid (LA, 18:2n-6) and α-linolenic acid (αLA, 18:3n-3), serve as the initial unsaturated precursors for the *in vivo* biosynthesis of the longer chain PUFAs. Metabolism of the EFAs in most tissues involves an alternating sequence of Δ^6 desaturation, chain elonga-

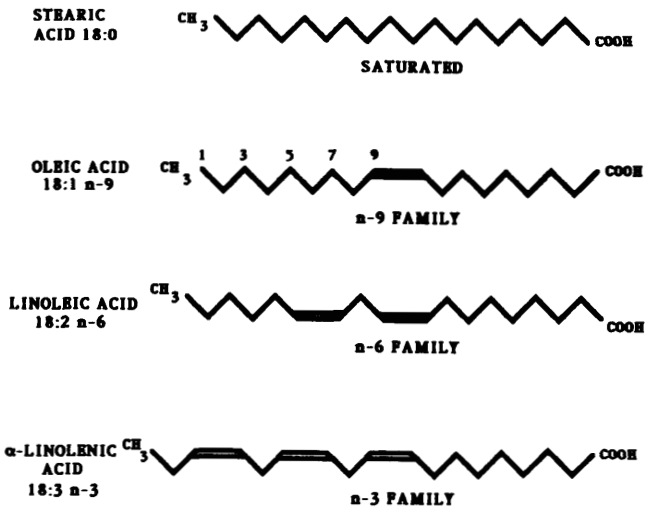

Figure 1. Representative structures of saturated, monounsaturated (n-9) and polyunsaturated (n-6 and n-3) fatty acids.

tion, and Δ^5 desaturation in which two hydrogen atoms are removed to create a new double bond followed by the addition of two carbon atoms to lengthen the fatty acid chain (4) (Fig. 2). The desaturations are catalyzed by two separate enzymes: the Δ^6 desaturase (catalyzing the transformation of 18:2n-6 to 18:3n-6) and the Δ^5 desaturase (catalyzing the transformation of 20:3n-6 to 20:4n-6). The elongase enzyme catalyzes the elongation of 18:3n-6 to 20:3n-6 dihomogammalinolenic acid (DGLA) (5). It is believed that the same enzymes catalyze equivalent steps in the n-3 and n-9 pathways (6). The PUFA families interact in such a manner that the n-3 acids competitively suppress the bioconversion of the n-6 acids, while the n-6 suppress the metabolism of the n-3 acids, although less markedly. Both the n-6 and the n-3 acids nonetheless do suppress the formation of the nonessential long chain n-9 acids, hence the negligible formation of the long chain n-9 PUFA (20:3n-9) in normally fed animals. In fact, the ratio of 20:3n-9 to 20:4n-6 (triene/tetraene ratio) of 0.4 is seen during EFA deficiency and is therefore used as a marker of EFA deficiency (7).

Elongation/Desaturation of 18-Carbon Polyunsaturated Fatty Acids in the Epidermis. The skin unlike the liver or brain lacks the ability to either desaturate the shorter chain 18-carbon 18:2n-6 (LA) into 18:3n-6 gammalinolenic acid (GLA), or to desaturate the longer chain 20 carbon dihomogammalinolenic acid (20:3n-6, DGLA) into 20:4n-6 (8, 9). Interestingly, the epidermis has a very active elongase activity. The elongase activity is present in human epidermis and does transform 18 carbon GLA into the 20 carbon DGLA (9). It is apparent from these studies that epi-

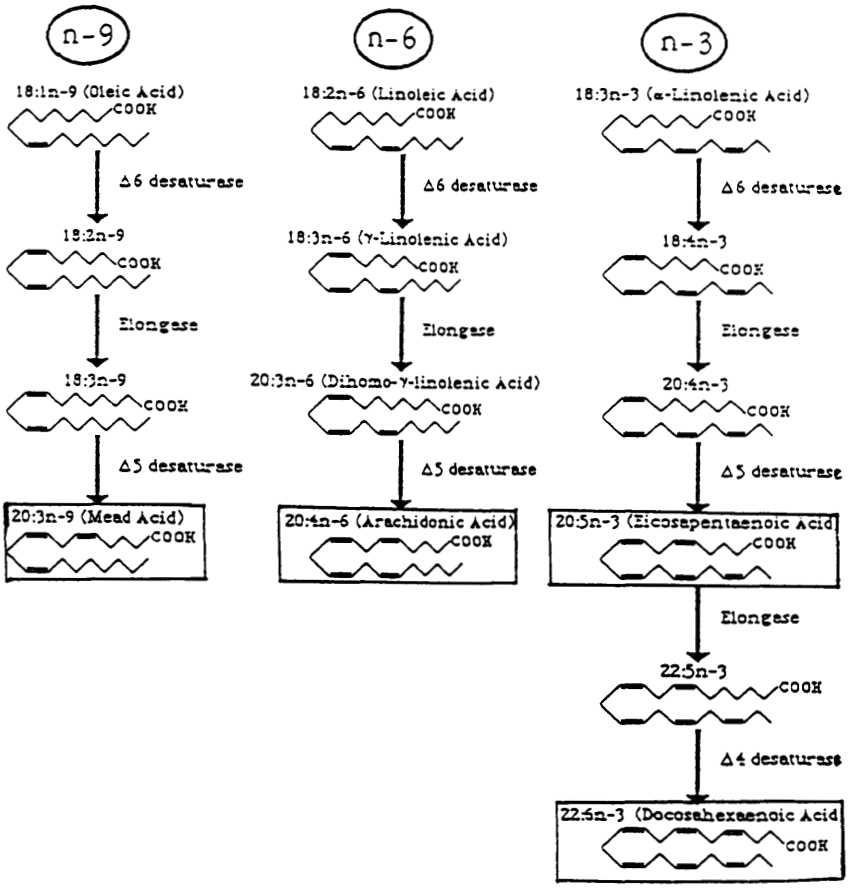

Figure 2. Oxidative desaturation and elongation of n-9, n-6 and n-3 polyunsaturated fatty acids.

dermal AA (the precursor for eicosanoids) is not biosynthesized locally from epidermal LA, consequently, the tissue depends on the contribution of AA from other endogenous sources. The mode of transport of AA to the epidermis is still not clear.

Functional Roles of 18 Carbon Fatty Acids in the Epidermis

Significance of Linoleic Acid in Epidermal Water Barrier System. The most abundant PUFAs in human skin are the 18-carbon linoleic acid (LA) and the 20-carbon arachidonic acid (AA) (9, 10). There is good evidence to indicate that one functional significance of the shorter 18-carbon LA is its involvement in the maintenance of the epidermal water barrier (11) which is one of the major abnormalities of cutaneous EFA deficiency. This significant effect of LA was reported early in a series of studies by Prottey and coworkers who demonstrated that increased transepidermal water loss (TEWL) occurred in EFA-deficient animals (12, 13, 14). Information derived from these findings supported the special role of LA in restoring the defect of epidermal water barrier which has been induced by EFA-deficiency. In latter reports, the physical structure of the epidermal water barrier was 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 (15) of which the linoleate-rich species have been characterized as acylglucosylceramide, acylceramide and a unique acylacid (16, 17, 18). More recently, it was suggested that the linoleyl moiety of the barrier acylsphingolipids is further metabolized by a lipoxygenase-like reaction to form first a hydroxyacyleramide and then a polyoxyacylceramide before the barrier function is exhibited (19). This finding prompted the group to propose that restoration of the defective epidermal water barrier system depended upon the formation of these oxygenated species. This view is consistent with the presence of a very active 15-lipoxygenase activity in the epidermis which converts LA (18:2n-6) into predominantly a 13-hydroxyoctadecadienoic acid (13-HODE) (20). It is very likely that this oxidative metabolite is the suggested oxygenated molecule of LA in the reported study. The precise oxygenated metabolite(s) involved in the above speculated barrier function have not been identified.

Significance of 13-hydroxyoctadecadienoic Acid (13-HODE) in Epidermal Hyperproliferation. Although the dietary feeding of LA to EFA-deficient animals reverses the two major cutaneous symptoms of EFA-deficiency which include hyperproliferation and increased transepidermal water loss, the mechanism for such a reversal has remained unknown. Since LA undergoes oxygenation into 13-HODE by epidermal 15-lipoxygenase, we explored a possible role for 13-HODE in a model of hyperproliferative skin. Specifically, severe hyperproliferation is induced in the skin of guinea pig by topical application of docosahexaenoic acid (22:6n-3 DHA). The hyperproliferation parallels a marked decrease of endogenous 13-HODE in the lesional epidermis, when compared to normal guinea pig skin (20). When 13-HODE is applied topically to the hyperproliferative lesional skin, tissue 13-HODE was restored to normal and the hyperproliferative skin was restored to normal. A further exploration into the possible mechanism of this antiproliferative effect revealed that the topically applied of 13-HODE was incorporated into epidermal phospholipids, notably, phosphatidylinositol 4,5-bisphosphate (PtdIns4,5-P_2). The incubation of the PtdIns 4,5-P_2 with epidermal phospholipase C resulted in the release and identification of a novel 13-HODE substituted DAG, (1-acyl-2-13HODE-glycerol). This occurrence suggests that a mode of action of 13-HODE, at least in part, may be via the inositol/phospholipid cascade/signal transduction system.

To ascribe a functional role to the newly formed 13-HODE-substituted DAG, 1-palmitoyl-2-13HODE-glycerol (13HODE-DAG) was synthesized and incubated with epidermal cytosol containing a mixture of protein kinase C (PKC) isoenzymes. The data revealed a striking inhibition of the total epidermal cytosolic protein kinase C activity. These findings suggest that 13-HODE reversal of epidermal hyperproliferation may be via the signal transduction/protein kinase C signaling pathway. A speculative scenario of the *in vivo* biosynthesis of 1-acyl-2-13HODE-glycerol (13HODE-DAG), and its modulation of PKC activity in the epidermis is illustrated in Figure 3. The association of the PKC inhibition and reversal of the skin hyperproliferation remains to be further elucidated.

Metabolism of 20-Carbon Polyunsaturated Fatty Acids in the Epidermis

The 20-carbon AA is also a prominent PUFA in the skin, and its functional role depends largely on its generation of biologically potent oxidative metabolites. The AA represents approximately 6%–10% of the total fatty acids in the epidermal phospholipids of guinea pigs (21, 22). Similarly, human skin contains approximately 9% of AA in the epidermal phospholipids (23). Specific epidermal enzymes metabolize AA into a variety of oxygenated metabolites, which in turn exert a variety of functions on the skin. For example, the AA metabolites function either to regulate proliferative or differentiating processes in the epidermis. Phospholipase A activity in the skin (24, 25) provides one of the mechanisms for the release of the PUFAs which are predominantly incorporated into epidermal

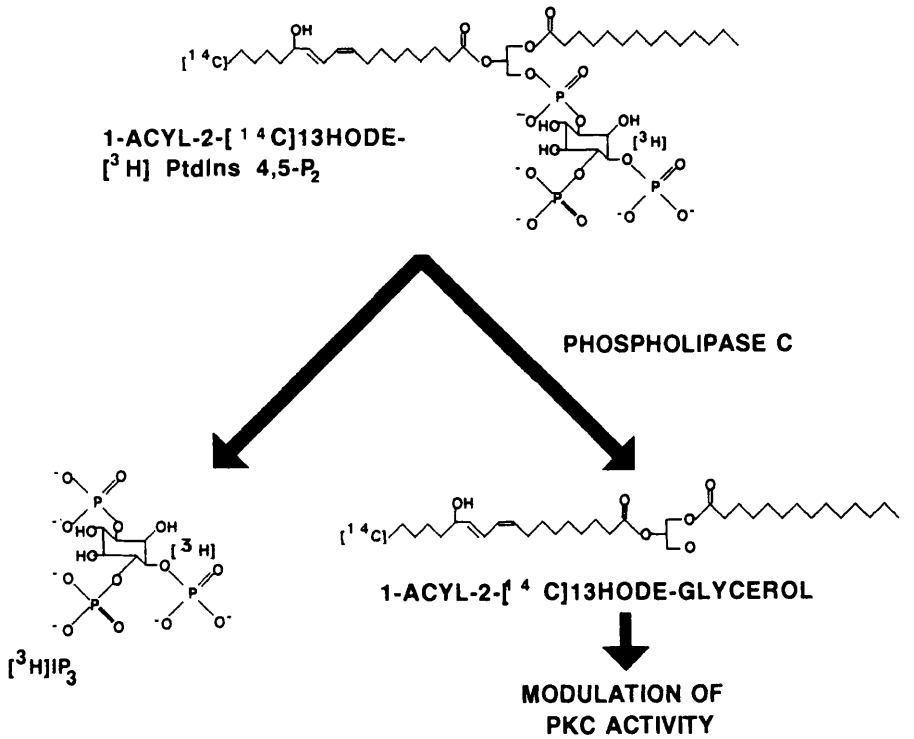

Figure 3. Speculative scenario of the incorporation of 13-HODE into PtdIns 4,5-P_2. Phospholipase C-catalyzed released of 13-HODE-DAG and its modulation of epidermal PKC activity.

phospholipids. Although the existence of a cytosolic phospholipase A_2 which is selective for cleavage (103) of arachidonic acid from phospholipids has been described, it is not known whether or not this is in the epidermis. However, the epidermal PUFAs when released undergo oxidative transformations either via the cyclooxgenase pathway to generate mainly prostaglandin E_2 (PGE_2), $PGF_{2\alpha}$, and PGD_2. It has recently been reported that PGD_2 is generated from arachidonic acid mainly by langerhan cells isolated from guinea pig epidermis (26) and from human epidermis (27). Thus, PGD_2 previously described in epidermis is probably localized in the langerhans cells. The significance of this prostanoid in the langerhans cells remains to be determined. The epidermal lipoxygenase pathway on the other hand, generates mainly hydroxy fatty acids. Although the epidermis cannot transform precursor arachidonic acid directly into leukotriene B_4 (LTB_4) because the epidermis expresses negligible 5-lipoxygenase activity, it can transform polymorphonuclear cell (PMN)-derived leukotriene A_4 (LTA_4) into LTB_4. This conversion of LTA_4 into LTB_4 is catalyzed by LTA_4-hydrolase (28, 29). The above possibility may explain the elevated LTB_4 in leukocyte-infiltrated cutaneous inflammatory reaction such as psoriasis.

Transformations via the Cyclooxygenase Pathway

The biosynthesis of cyclooxygenase products, mainly prostaglandins: PGE_2, PGF_α, and PGD_2 from AA has been well documented in skin preparations from rats (30), mice (31), guinea pigs, and humans (32–34). The enzymes which catalyze the biosynthetic activities are located primarily in the epidermal membrane and concentrated in the microsomal fraction (33). The overall biosynthesis of prostanoids from AA via the cyclooxygenase is illustrated in Figure 4. The initial enzymatic transformation of arachidonic acid into prostaglandin endoperoxide (PGH_2) is now be-

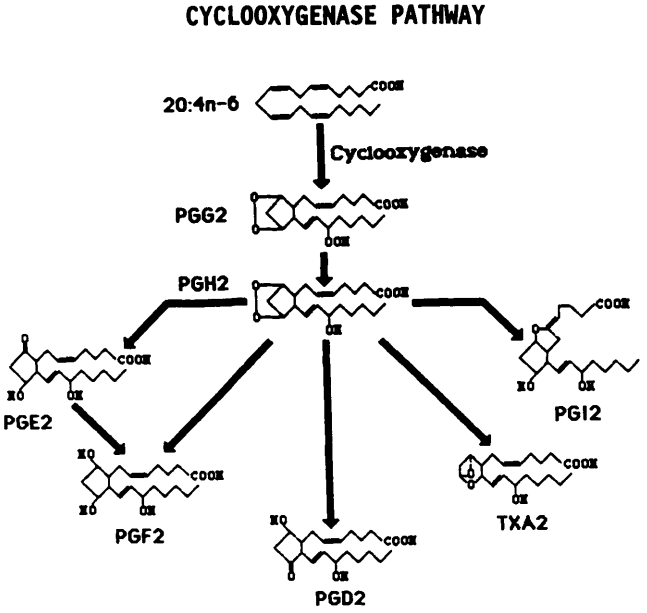

Figure 4. Metabolism of arachidonic acid via the cyclooxygenase pathway.

lieved to be catalyzed by two isozymes: PGH_2-synthase I (PGHS-I)/cyclooxygenase (Cox I), which was initially purified and cloned from sheep vesicular gland (35–40). This enzyme is constitutively expressed in a variety of tissues (41). In contrast, the PGH_2-synthesase 2 (PGHS-2)/Cox 2, which shares some amino acid identity with PGHS-I, is expressed only after cell activation (42, 43). On the other hand, the expression of PGHS-2 was reported to be stimulated by inflammatory mediators and immune cells and on the other, it is inhibited by glucocorticoids (44–46). Taken together, it appears that PGHS-2 may catalyze the generation of prostanoids associated with inflammation and/or mitogenesis. A differential inhibition of PGHS-I and PGHS-2 isozymes by common nonsteroidal anti-inflammatory drugs (NSAIDs) has recently been reported (47). Investigation into the expressions and roles of these PGHS-isozymes in cutaneous inflammatory/proliferative disorders have not been determined but would seem an interesting line of investigative pursuit so as to elucidate the mode of action of the anti-inflammatory glucocorticoids commonly used in cutaneous inflammatory diseases.

Functional Roles of Cyclooxygenase Products (Prostaglandins) in the Skin

Prostaglandins as Possible Mediators of Inflammation. The prostaglandins play a central and complex role in inflammation and therefore are pertinent to the pathogenesis and treatment of cutaneous inflammatory diseases. For example, it was reported very early that prostaglandins of the E-series (PGE_1) and PGE_2 stimulated collagen biosynthesis (48) and thus were associated with increased collagen formation known to occur with persisting inflammation. In other studies, repeated injections of PGE_2 were reported to cause a persistent swelling of the rodent paw which interfered with ambulation (49). Similarly, the injections of PGE_1 and PGE_2 into the knee joints of dogs also resulted in severe disabling arthritis (50). Repeated injections of PGE_1 into human skin resulted in cutaneous inflammatory reactions characterized by erythema, edema, and tenderness (51). These early findings, although interesting, were flawed, because the concentrations of PGs used in many instances were high and well above physiological levels. Nonetheless, the beneficial effects derived from administration of nonsteroidal anti-inflammatory drugs (NSAIDs) did implicate some of these prostanoids in the cutaneous inflammatory processes (52).

Prostaglandins in Ultraviolet Light Irradiation (UVL)-induced Abnormalities. Erythema is the most conspicuous and most easily evaluated response of skin to ultraviolet light irradiation, particularly, ultraviolet B (UV-B) irradiation, hence the immense interest in delineating the time course of the synthesis of the prostaglandin mediators and their roles in UVL-induced inflammatory reactions. The use of indomethacin (an inhibitor of arachidonic acid oxygenation via the cyclooxygenase pathway), first provided strong evidence of possible involvement of the prostaglandins in the UVB-induced erythema (53, 54). These studies with cyclooxygenase inhibitors were followed by measurements of endogenous levels of PGs released into suction blister fluids after UV-B irradiation (25–58). A correlation between PGs formed and erythema was demonstrated during the first 24 hr after UVB-irradiation. However, at 48 hr the endogenous levels of PGs returned to normal, while the erythema remained discernible. This finding suggested that other mediators, not PGs, are contributors to the late and persisting erythema. To explain the puzzle of the sustained erythema after 24 hr, which could not be alleviated by indomethacin, new studies were conducted to test whether products of the lipoxygenase pathway could be involved. Such a follow-up study indicated that lipoxygenase products of arachidonic acid, particularly, the monohydroxy fatty acids: 12-hydroxy-eicosatetraenoic acid (12-HETE) and 15-hydroxy-eicosatetraenoic acid (15-HETE), are generated beyond 24 hr after UVB-irradiation. Thus, the mediators derived from lipoxygenase pathway could be involved in the sustained erythema beyond 24 hr (41). This might explain the persistence of erythema despite the intake of indomethacin, which is a more selective inhibitor of cyclooxygenase pathway. Recent reports that the transformation of arachidonic acid into prostaglandins is catalyzed by two PGHS-isozymes and that they exhibit selectivity in response to indomethacin and other NSAIDs (47) raise the possibility that these isozymes may be expressed during UVB-induced cutaneous inflammation and complete suppression of the immediate and long-term inflammatory reactions may require the suppression of both isozymes.

Prostaglandins in Epidermal Tumorigenesis. Although the prostaglandins are well linked to the inflammatory processes in the skin, their roles in epidermal tumorigenesis have been less clear, since they depend largely on concentrations involved. Nonetheless, there is considerable evidence that prostaglandins may be involved with tumorigenesis based on the model of 12-0-tetradenoylphorbol-13-acetate (TPA)-induced skin hyperplasia. For instance, TPA is reported to induce the release of arachidonic acid and prostaglandins in the skin (60). Some earlier findings revealed that the pretreatment of mouse skin with a cyclooxygenase inhibitor (indomethacin), markedly inhibited the induction of epidermal ornithine decarboxylase activity (a marker for hyperproliferation and DNA synthesis). The generation of ODC at the time was taken

as the typical and prominent biochemical alteration elicited by TPA. Furthermore, it was also reported that topical application of prostaglandin E_2 (PGE_2) to the skin overrides the inhibitory effect of indomethacin on ODC induction. These observations prompted the earlier suggestions that PGE_2 may play a crucial role in ODC induction by TPA.

In another model, the role of prostaglandins in the skin of chemically-induced carcinogenesis was suggested in the multistage model of skin carcinogenesis. The carcinogenesis was induced after topical application of 7,12-dimethylbenz (a) anthracene (DMBA), a potent carcinogen. In the initiation-promotion stages of the chemically-induced mouse skin tumorigenesis (61), prostaglandins were reported to enhance tumor formation (62, 63). Blockade of the epidermal metabolism of AA by indomethacin was shown to inhibit tumor development (64, 65). One possible mechanism for the prostaglandin involvement in chemically-induced carcinogenesis was postulated to occur during the co-oxygenation of the chemical carcinogen on the one hand, by epoxidation reactions of the carcinogens into epoxides (66) by cytochrome P450 and on the other hand, during the oxygenation of AA into hydroperoxy endoperoxide (PGG_2) by prostaglandin H-synthase (67). The resulting endoperoxide is then reduced by a peroxidase activity (resident in the same enzyme polypeptide) to hydroxy endoperoxide (PGH_2). The resultant effect of the co-oxygenation of AA and the carcinogen is the generation of electrophylic derivatives of polycyclic aromatic hydrocarbons from the carcinogen which bind to protein and DNA and thus induce mutagenicity.

Transformations via Lipoxygenase Pathways

Oxygenation of Arachidonic Acid (20:4n-6) via the 12-Lipoxygenase Pathway. The lipoxygenase pathway is very active in the epidermis. For instance, the 12-lipoxygenase product of AA, 12-L-hydroxy-eicosatetraenoic acid (12-HETE) was first reported to accumulate in the lesion of psoriatic patients (34). This observation provoked the first interest in the possible role of this monohydroxy fatty acid in cutaneous homeostasis. Although 12-HETE can exert moderate inflammatory effects in a variety of cell types, its full significance in epidermal inflammatory/proliferative processes is not fully understood. Advances in chiral phase chromatography now reveal that 12-HETE which originally (34) was reported to accumulate in the lesion of psoriatic patients is primarily the 12(R) epimer and not the 12(S) epimer that is the typical 12-lipoxygenase product form in platelets (68). The 12(R)-HETE has been shown to be more potent than 12(S)-HETE as a chemo-attractant. It has recently been reported that 12(R)-HETE and 12(S)-HETE are products of an epidermal membrane-bound monoxygenase (69).

Oxygenation of Arachidonic Acid (20:4n-6) via the 15-Lipoxygenase Pathway. The 15-lipoxygenase enzyme, on the other hand, is very active in the epidermis. Products of the variety of polyunsaturated fatty acids (PUFAs) which are generated via this pathway yield biologically active metabolites in this tissue. For example, the 15-hydroxyeicosatetraenoic acid (15-HETE), a product derived from AA, has been demonstrated in human epidermis (70), in cultured murine and human epidermal cells (keratinocytes), in isolated human neonatal foreskin (71) and in guinea pig epidermis (72). This monohydroxy fatty acid was detected in biologically active concentrations in human patients with psoriatic lesions (72, 73). Although attempts to stimulate keratinocytes in culture with calcium ionophore to release 15-HETE into the medium have met with limited success, probably due to the use of inappropriate agonists, 15-HETE has been extracted and demonstrated *in vivo* in the epidermis (74) where it is esterified to the phospholipids.

Functionally, 15-HETE *in vitro* was reported to inhibit 5-lipoxygenase activity and generation of LTB_4 in neutrophils and basophils (75). Similarly, 15-HETE generated from epidermis from AA has also been shown to inhibit the generation of 12-HETE from AA (76). These *in vitro* effects suggest, at least in part, the anti-inflammatory potential of 15-HETE. Consistent with this anti-inflammatory potential, 15-HETE was reported to improve the symptoms of psoriasis vulgaris after intralesional injections (77). Although the mechanism of this antilesional effect is unclear, one possibility is that 15-HETE in pharmacologically active doses may function *in vivo* to inhibit the formation of products of 5- and 12-lipoxygenases (LTB_4 and 12-HETE), both of which are markedly elevated in the psoriatic lesion. It is therefore, reasonable to speculate that an elevation of this monohydroxy fatty acid in the epidermis may provide a local *in vivo* anti-inflammatory molecule which will inhibit AA-derived inflammatory metabolites.

Oxygenation of Other Polyunsaturated Fatty Acids via 15-Lipoxygenase Pathway

Metabolism of Dihomogammalinolenic Acid (20:3n-6). The dihomogammalinolenic acid (DGLA) is an elongation product of γ-linolenic acid (18:3n-6), a Δ^6 esaturation product of linoleic acid (18:2n-6). DGLA is metabolized by epidermal cyclooxygenase enzymes into prostaglandin of the 1-series (PGE_1). It is found in small amounts in normal epidermis (21). The guinea pig epidermis, as well as human epidermis, contains very active elongase that catalyzes the conversion of precursor GLA (18:3n-6) into DGLA (20:3n-6) (9). Supplementation of guinea pig diet (22) with prim-

rose oil (a vegetable oil that contains GLA) significantly increases the epidermal levels of DGLA, its cyclooxygenase pathway metabolite prostaglandin E_1, and its lipoxygenase pathway metabolite, 15-hydroxy-eicosatrienoic acid (15-HETrE). Since primrose oil has been used in the clinical management of inflammatory/hyperproliferative disorders of the skin (78, 79), its reported beneficial effects may be due, at least in part, to epidermal cyclooxygenase pathway generation of prostaglandin E_1 (PGE_1) from DGLA and the generation of 15-hydroxy-eicosatrienoic acid (15-HETrE) via the lipoxygenase pathway from elevated tissue DGLA. The 15-HETrE is a potent inhibitor of proinflammatory LTB_4 biosynthesis from PMNs *in vitro* (76). Interestingly, 15-HETrE was found to be more potent than 15-HETE derived from AA and the other monohydroxy fatty acids, such as 15-HEPE (15-hydroxyeicosapentaenoic acid) and 17-HoDHE (17-hydroxyeicosahexaenoic acid) derived from fish oil polyunsaturated fatty acids (80).

Oxygenation of Eicosapentaenoic Acid (20:5n-3) and Docosahexaenoic Acid (22:6n-3) via the 15-Lipoxygenase Pathway. Eicosapentaenoic acid (20:5n-3, EPA) and docosahexaenoic acid (22:6n-3, DHA) are the two major PUFAs derived from fish oils. The *in vitro* incubation of eicosapentaenoic acid or docosahexaenoic acid with epidermal preparations as well as dietary ingestion of fish oils results in the epidermal formation of two 15-lipoxygenase products: 15-hydroxyeicosapentaenoic acid (15-HEPE) and 17-hydroxydocosahexaenoic acid (17-HoDHE) respectively (81, 82). Both metabolites are potent inhibitors of LTB_4 formation from PMNs *in vitro*.

Taken together, 15-lipoxygenase catalyzed metabolites derived from both the n-6 PUFAs (AA and DGLA) and the n-3 PUFAs (EPA and DHA) exert varying degrees of dose-dependent inhibitory effects on the *in vitro* generation of LTB_4 (80). Interestingly, 15-HETrE (the metabolite derived from DGLA) exerts the most potent inhibitory effect when compared to the other monohydroxy acids derived from 20- and 22-carbon PUFAs. In contrast, the 18-carbon 13-hydroxyoctadecadienoic acid (13-HODE) derived from LA which exerts very moderate anti-inflammatory effects *in vitro,* does exert an antiproliferative effect when topically applied to epidermal lesion (20). These findings underscore the emerging recognition that 15-lipoxygenase monohydroxylated metabolites generated from the PUFAs may play important roles in cutaneous biology.

Oxygenation of Arachidonic Acid (20:4n-6) via Epidermal 5-Lipoxygenase Pathway

The 5-lipoxygenase pathway generates mainly leukotrienes: LTB_4, LTC_4, and LTD_4 from AA by leukocytes. These metabolites are known to accumulate in the lesions of psoriasis (83, 84), prompting controversy as to their *in vivo* source. Because the psoriatic lesion is infiltrated with leukocytes (particularly, the PMNs) one possibility is that these leukocytes contribute largely to the leukotrienes found in the psoriatic lesion. However, there is now new information which indicate that some of the leukotrienes in the psoriatic lesion are synthesized locally by the epidermis. For example, the incubation of human epidermal preparations with PMN-derived LTA_4, or the co-incubation of human PMNs with keratinocytes in culture, results in the generation of LTB_4 (28, 29). These studies underscore the possibility that keratinocytes may amplify local LTB_4 formation by utilizing PMN-derived LTA_4 during cutaneous inflammation when PMNs migrate into the epidermis as in psoriasis.

The leukotrienes are known to exert a variety of effects on a variety of cells. For instance, when LTB_4 is tested on cells *in vitro,* it exerts a potent chemoattractant effect for neutrophils (85), eosinophils and neutrophils (49, 86), and fibroblasts (87). Notably, LTB_4 induces chemotaxis and chemokinesis at very low concentrations. Intradermal injection of LTB_4 into skin induces transient weal, flare, and erythematous induration (88, 89). Topical application of LTB_4 to skin induces intraepidermal microabcesses (90) and epidermal proliferation in guinea pig (91) and human skin (92). These effects implicate LTB_4 as an important mediator in cutaneous inflammatory and proliferative disorders. Transformations of AA via the lipoxygenase pathways are illustrated in Figure 5.

Regulation of Epidermal Biosynthesis of Cyclooxygenase and Lipoxygenase Products

Pharmacological Regulation of Eicosanoid Generation. It is evident from accumulating findings that oxidative metabolites generated from AA (PGs, leukotrienes, and hydroxy fatty acids) may be of profound clinical importance in dermatology. Interestingly, while some of these metabolites are proinflammatory, others are anti-inflammatory. Thus, pharmacological inhibitors of proinflammatory PG and leukotriene synthesis, and antagonists of endogenously biosynthesized inflammatory mediators, could become important front line agents or adjuncts in the future treatment of cutaneous inflammatory skin disorders. Consistent with this view, the use of anti-inflammatory inhibitors has already resulted in better understanding of the efficacy of pharmacologically active substances in modulating the pathways that generate inflammatory mediators. Pharmacological agents that are targeted towards specific cyclooxygenase or lipoxygenase pathways are likely to be more fruitful than those with non-selective pathways. A number of 5-lipoxygenase inhibitors and antagonists selective for specific leukotrienes have been synthesized for the

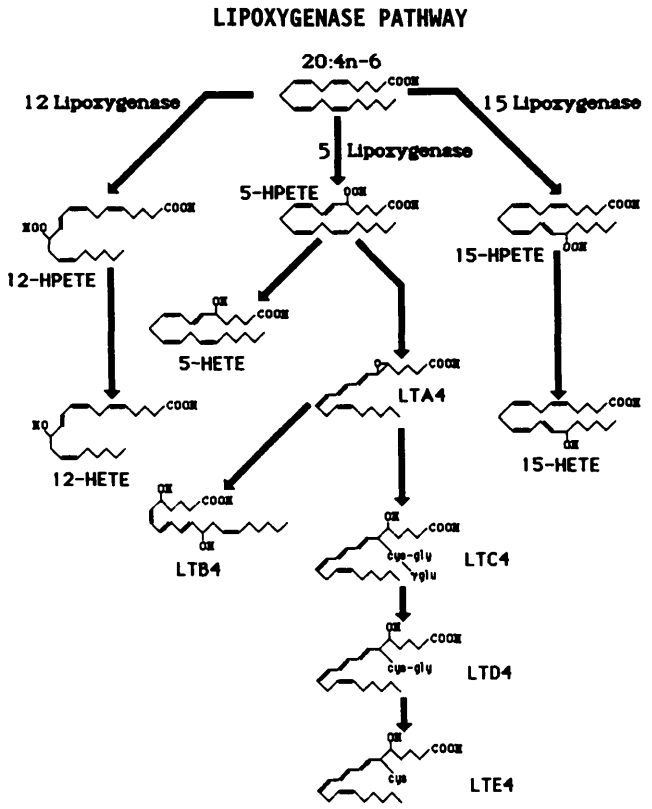

Figure 5. Metabolism of arachidonic acid via the lipoxygenase pathway.

possible management of some inflammatory/proliferative skin disorders. Their widespread use has been limited because of undesirable side effects.

Dietary Regulation of Eicosanoid Generation. While pharmacological agents are effective, their beneficial effects are tempered by undesirable side effects. Since the precursor of the variety of eicosanoids are derived from dietary sources, it is reasonable to expect that the *in vivo* synthesis of the mediators can be modulated by manipulation of the diets. For example, the supplementation of diets of psoriatic patients with fish oil which contains two n-3 polyunsaturated fatty acids: eicospentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to moderately alleviate the symptoms of psoriasis (93–97). This efficacy thus provides an alternative protocol for the management of psoriasis. The efficacy of these dietary studies are compatible with the view that diet supplemented with EPA- and DHA-enriched oils can exert profound effects on endogenous epidermal phospholipid fatty acid compositions, as well as on the endogenous release of AA and biosynthesis of the inflammatory eicosanoids. Specifically, the dietary intake of fish oil has been shown to result in elevated levels of EPA and DHA in epidermal phospholipids. The incorporation of EPA and DHA in the tissue is paralleled by elevated levels of endogenous biosynthesis of 15-hydroxy-eicosapentaenoic acid (15-HEPE) and 17-hydroxydocosahexaenoic acid (17-HoDHE), both metabolites of EPA and DHA catalyzed by epidermal 15-lipogenase. Since these metabolites possess potent inhibitory effects on neutrophil generation of proinflammatory LTB_4 *in vitro,* it is reasonable to speculate that their elevation in the epidermis after dietary intake of fish oil would result in the inhibition of local biosynthesis of LTB_4 by leukocyte and epidermis. There is also an interesting relationship between the amount of ingested precursor PUFA and the amount of *in vivo* generation of endogenous anti-inflammatory metabolites, a factor that must be considered in dietary supplementation of diets with fish oil. Thus, the dietary supplementation with highly purified fish oil or its ethyl esters can serve at least as an adjunct to standard regimens in the management of skin inflammatory disorders.

Similarly, excitement was generated by reports of clinical improvement of patients with atopic eczema after oral administration of primrose oil (78, 79). These reports signalled a possible role of GLA-containing vegetable oils in cutaneous biology since epidermis possesses an active elongase enzyme but negligible Δ^5 desaturase activity. For example, orally administered evening primrose oil (EPO) increased tissue levels of prostaglandins of the 1-series (PGE_1) and suppressed chronic inflammation (98, 99). This beneficial effect is probably due to the *in vivo* metabolism of primrose GLA into DGLA and its subsequent oxygenation via the cyclooxygenase pathway into PGE_1. The biological activity of PGE_1 had previously been reported to suppress the inflammations associated with rodent adjuvant arthritis (100) and immune complex vasculitis (101). Furthermore, the epidermal increase in DGLA is paralleled by epidermal increase in the levels of 15-HETrE (a 15-lipoxygenase metabolite of DGLA) (102). The monohydroxy fatty acid (15-HETrE) is a potent inhibitor of LTB_4 formation *in vitro.* Taken together, dietary supplementation of GLA-containing oils could serve as a monotherapy or as an adjunct in the management of certain forms of cutaneous inflammatory disorders.

A speculative scenario of the possible modulatory effects of the constituent fatty acids and metabolites from vegetable and fish oils on the generation of proinflammatory leukotrienes from AA is shown in Figure 6. Pathway A illustrates the metabolic transformations from dietary intake of safflower oil (rich in LA) which include the *in vivo* desaturation and elongation of LA into AA; the 5-lipoxygenation of AA into proinflammatory leukotrienes (particularly leukotriene B_4) by polymorphonuclear cells (PMNs). Pathway B represents the epidermal metabolic transformations of dietary intake of vegetable oils rich in GLA (primrose oil and borage oil); the *in vivo* elongation of GLA into DGLA; and the local epidermal transformation of

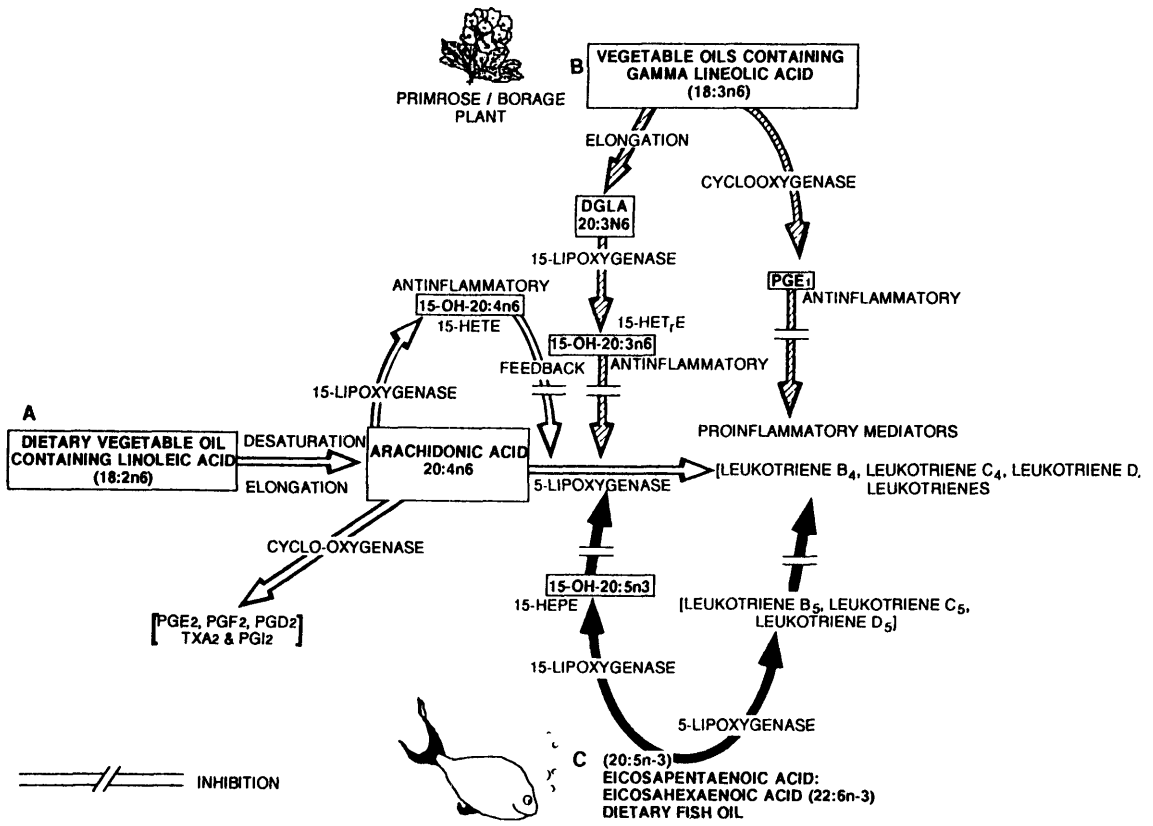

Figure 6. A speculative scenario of the possible modulatory effects of the constituent fatty acids and metabolites from vegetable and fish oils on the generation of proinflammatory leukotrienes from AA.

DGLA into both 15-HETrE via the 15-lipoxygenase pathway and PGE_1 via the cyclooxygenase pathway. Pathway C represents the metabolic transformations of dietary intake of fish oil rich in EPA and DHA and the *in vivo* metabolism of EPA into 15-HEPE via the 15-lipoxygenase. It is reasonable to speculate that metabolites from both pathways B and C could in turn inhibit the *in vivo* generation of local tissue proinflammatory leukotrienes from AA in the epidermis. These *in vivo* possibilities imply that the dietary intake of highly purified vegetable or fish oils, or the intake of the appropriate constituent PUFAs from these oils, may offer an alternative therapeutic modality for alleviating cutaneous inflammatory disorders.

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