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ESSENTIAL FATTY ACIDS AND POLYUNSATURATED FATTY ACIDS: Significance in Cutaneous Biology

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CONTENTS

INTRODUCTION

The skin represents the outermost portion of the mammalian body and performs a variety of functions including the formation of melanin, the photo-

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induced synthesis of vitamin D_3, the production of sebum, and the keratinization of epidermal cells. The skin consists of three layers: the epidermis, the dermis, and the subcutaneous (adipose) tissue. Although the subcutaneous fatty tissue is considered a part of the skin, its contribution to the overall biology of skin has not been fully delineated. A schematic diagram of a cross-section of human skin is shown in Figure 1.

Overlying the subcutaneous tissue at the lowest portion of the diagram is the dermis, whose principal function is to provide the upper epidermal layer with physical and nutritional support. The dermis has a well-developed upper papillary layer and a lower deep reticular layer that are well supplied by

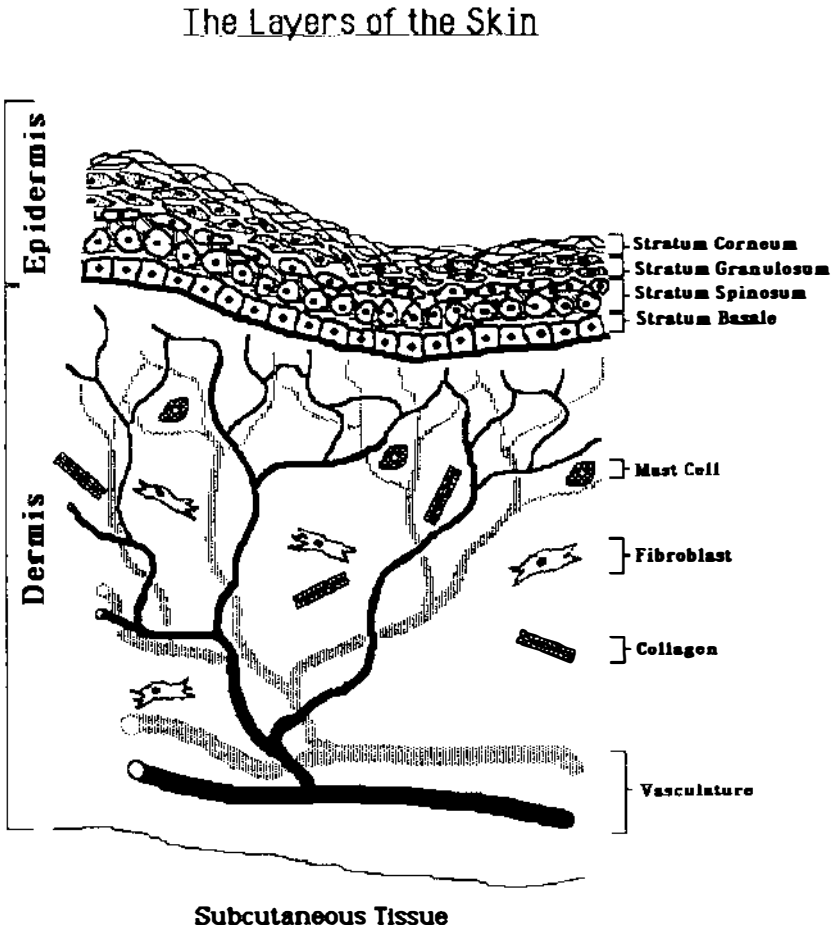

Figure 1 A schematic drawing of the cross-section of skin showing the major layers and appendages.

capillaries meshed in delicate collagenous fibers. The epidermis is nourished by the papillae. The lower reticular layer is primarily composed of coarse collagen bundles and elastin fibers embedded in a nonfibrous, semifluid ground substance that reportedly consists largely of glycosaminoglycans. The predominant cells in the dermis are fibroblasts that elaborate both extracellular fibrous proteins and nonfibrous ground substance. The dermis also contains mast cells that elaborate local mediators.

The uppermost segment of the skin, the epidermis, is composed of several distinct layers of different cells. The lowest cellular layer is the *stratum basale*. Cells in this layer periodically divide and the daughter cells move upwards toward the surface of the tissue to acquire spinous processes forming the next layer, the *stratum spinosum*. The thickness of this layer varies in different animals. As the cells in the *stratum spinosum* ascend upwards they form layers and accumulate keratohyaline granules to form the granular layer, or *stratum granulosum*. During the upward transit of these cells, keratin is synthesized as well as complex lipids (acylsphingolipids) that are secreted to the cell surface, the *stratum corneum*. The body surface consists of dead horny cells composed of keratin. Because these processes are continuous and in a dynamic state, the epidermis represents a skin segment of both active proliferation and differentiation.

THE ESSENTIALITY OF DIETARY FAT

The first indication that dietary fat may be essential for healthy growing animals was presented by Aron in 1918. He proposed that butter has a nutrient value that cannot be provided by other dietary components (2). In this report he suggested that, apart from its caloric contribution, fat had an inherent nutritive value that was possibly related to the presence of certain lipids. In 1920, Osborne & Mendel, while studying the essentiality of vitamin A (43), cited the role of fat as a carrier of this fat-soluble nutrient. By 1927, major improvements in the use of purified fat-free diets enabled Evans & Burr to demonstrate that a dietary deficiency of fat severely affected both growth and reproduction of the experimental animals even though the known fat-soluble vitamins (A, D, and E) were supplied in excess (17). Further experiments led Evans & Burr to conclude that "the favorable substance in fats is possibly a new vitamin (F), which unlike vitamins A, D, and E, is not concentrated in the nonsaponifiable fraction of the dietary extract" (18).

In 1929, Burr & Burr (9) 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 (LIN, 18:2n-6[1]) was heralded as an "essential fatty acid" (EFA) (10). This pioneering study observed that in addition to the visible scaliness of their skin, animals with essential fatty acid deficiency (EFA-deficiency) also experienced increased water consumption without increased urine output, which led to speculation of increased water loss through the skin. Thus, in these early studies, Burr & Burr recognized the two major defects associated with EFA deficiency in cutaneous biology, namely (*i*) epidermal hyperproliferation and (*ii*) increased permeability of the skin to water.

BIOCHEMISTRY OF EFA

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 2. 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.

Dietary Sources

The 18-carbon n-6 and n-3 PUFAs are synthesized on land by many plants and therefore are dietarily 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 meat, which are rich dietary sources for arachidonic acid.

[1]Fatty acids and acyl groups are denoted 18:2n-6, 18:3n-3, and so on; the first number represents the number of carbons in the acyl chain, the number following the colon indicates the number of methylene-interrupted *cis* double bonds, and the number of "n" indicates the number of carbon atoms from the methyl end of the acyl chain to the nearest double bond.

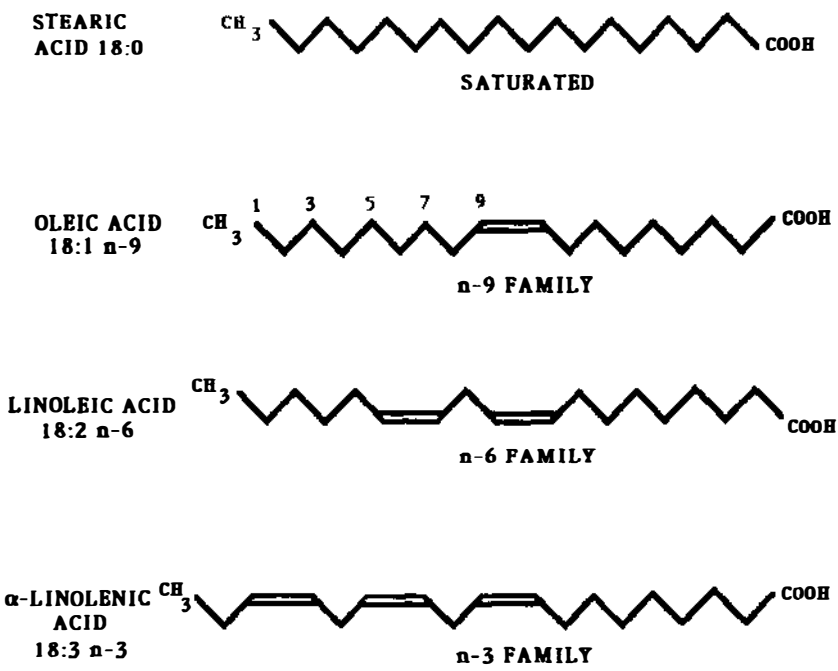

Figure 2 Representative structures of saturated, monounsaturated (n-9), and polyunsaturated [(n-6) and (n-3)] fatty acids.

Metabolism of Shorter Chain EFAs in Mammalian Systems

The shorter chain EFA's, 18:2n-6 and alphalinolenic 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 elongation, 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 (35). 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) (21). It is believed that the same enzymes catalyze equivalent steps in the n-3, and n-9 pathways (7). 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 acids 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 20:3n-9 to 20:4n-6 (triene/tetraene ratio) of 0.4 is used as a marker of EFA deficiency (40).

Desaturation and Elongation of PUFA in the Epidermis

The skin, unlike the liver or brain, lacks the ability to either desaturate 18:2n-6 into 18:3n-6 or desaturate 20:3n-6 into 20:4n-6 (13, 14). Interestingly, the epidermis has a very active elongase activity, and thus preparations from human epidermis reportedly transform 18-carbon GLA into the 20 carbon DGLA (14). A schematic illustration of the oxidative desaturation and chain elongation of essential fatty acids by human epidermal preparations is shown in Figure 3. It is apparent from these studies that epidermal AA (a precursor for eicosanoids) is not biosynthesized locally from epidermal LIN; consequently, the tissue depends on the contribution of AA from other endogenous sources.

FUNCTIONAL ROLE OF POLYUNSATURATED FATTY ACIDS IN THE SKIN

Role in Epidermal Water Barrier System

The most abundant PUFAs in human skin are LIN and AA (14, 59). Substantial evidence now exists that at least one essential function of LIN in the skin is to maintain the integrity of the epidermal water barrier (24). The Burrs' observations of increased water consumption by EFA-deficient animals without increased urinary output only indicated an increase in water loss from the EFA-deficient animals without specifically assigning this symptom to a skin disorder (10). Basnayake & Sinclair were the first to demonstrate a defect in the ability of the skin to act as an effective water barrier in EFA-deficient animals (3, 4). The advent of equipment specifically designed to measure water loss from selected areas of the skin allowed investigators to record trans-epidermal water loss (TEWL) in human skin under a variety of dermatological conditions (22). In a series of studies, Prottey and co-workers used such a device to firmly establish increased TEWL in EFA-deficient animals (25, 44–46). Information derived from these experiments supported the special role of LIN in correcting TEWL that had been induced by EFA-deficiency.

The concept that LIN is essential in the maintenance of the epidermal barrier system has led researchers to focus on the isolation of LIN from certain epidermal acylsphingolipids. Sweeney & Downing confirmed the importance of lipids in the epidermal water barrier by demonstrating increased water diffusion in skin treated with lipid-removing solvents (50). The physical structure of the epidermal water barrier was ascribed to sheets of stacked lipid

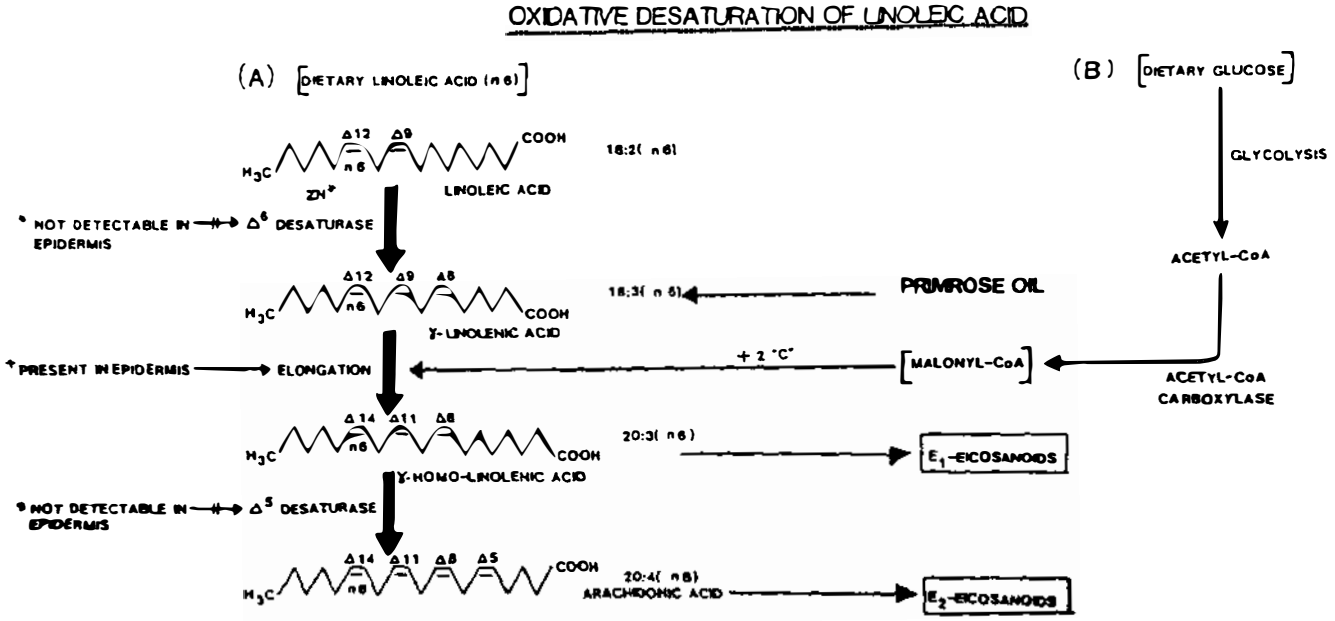

Figure 3 Oxidative desaturation and elongation in the skin.

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 (16), of which the linoleate-rich species have been characterized as acylglucosylceramide, acylceramide, and a unique acylacid (1, 5, 54). In EFA-deficiency, the linoleic acid in the ceramides is replaced by oleic acid (53), which results in severe water loss from the skin of these animals. Interestingly, Nugteren et al (42) have demonstrated that the linoleyl moiety of the barrier acylsphingolipids must be further metabolized before the barrier function is exhibited. Specifically, these investigators showed that the acylceramide components of the epidermal water barrier may undergo oxygenation by the action of a lipoxygenase-like reaction to form first a hydroxyacylceramide and then a polyoxyacylceramide. They therefore proposed that restoration of the defective epidermal water barrier system depended upon the formation of these oxygenated species. Possibly, the ability of LIN to maintain the integrity of the epidermal water barrier is dependent upon lipoxygenase activity; this hypothesis is interesting because the epidermal lipoxygenase product of linoleic acid, 13-hydroxyoctadecadienoic acid (13-HODE), is involved in regulating epidermal proliferation.

Role in Epidermal Proliferation

After the pioneering studies of Burr & Burr (9) revealed that animals deficient in EFA manifest severe scaliness of the skin, efforts were made to associate this scaliness with epidermal hyperproliferation. The early studies by Holman (26), Worby (57), and Prottey (44) indicated the possibility of skin hyperproliferation but were unable to quantitatively measure epidermal proliferation. Conclusive evidence of epidermal hyperproliferation as a feature of EFA deficiency was provided by the radiolabeling of cycling epidermal cells with tritiated thymidine to estimate DNA synthesis (36, 37).

A number of PUFAs have been used to reverse the scaliness and hyperproliferation caused by EFA-deficiency. For example, in the early experiments of Burr (8), the 18-carbon chain LIN and 20-carbon chain AA were reported to reverse the scaliness and growth abnormality characteristics of EFA-deficiency, whereas saturated fatty acids and a monoene (oleic acid) failed to reverse the symptoms. More recently, LIN was reported to be more effective than AA (15). These investigators showed that the dietary induction of epidermal hyperproliferation in EFA-deficient guinea pigs paralleled the marked decrease of LIN in the epidermal lipids while the level of AA remained relatively unchanged. In these studies the symptoms of EFA-deficiency were reversed by supplementation of the diet of the EFA-deficient animals with either of two vegetable oils containing n-6 PUFAs: safflower oil containing predominantly LIN (78%) or evening primrose oil (EPO) containing both LIN (73%) and GLA (9%). In contrast, supplementation of the

EFA-deficient animals with n-3 PUFA-rich fish oil, which contained LIN (1.2%), EPA (16.9%), and DHA (12%), was ineffective.

Physiological Role of n-3 Polyunsaturated Fatty Acids

Unlike the role of the n-6 PUFAs, the physiological role of the n-3 PUFAs in the biology of skin is not clear. To explore whether or not the n-3 PUFAs exert a physiological effect on skin, the diet of normal guinea pigs was supplemented with fish oil. An interesting finding is the incorporation of the n-3 PUFAs (EPA and DHA) into specific epidermal phospholipids (39). For instance, dietary EPA was incorporated mainly into epidermal phosphatidylcholine (PC), with lesser amounts found in phosphatidylethanolamine (PE) and phosphatidylinositol/phosphatidylserine (PI/PS). In contrast, DHA was preferentially incorporated into PE and none was incorporated into PC. The significance of these preferential distributions into selected phospholipids and the turnover of these pools of phospholipids remains to be determined. Coincident with the uptake of the n-3 PUFAs into the epidermal phospholipids is the elevation of epidermal levels of 15-hydroxyeicosapentaenoic acid (15-HEPE), which is catalyzed by the 15-epidermal lipoxygenase in vivo. Although DHA was incorporated into epidermal phospholipid (PE), its epidermal metabolite 17-hydroxydocosahexaenoic acid (17-HDoHE) was detected in the epidermis only after the intake of high concentrates of fish oil. This latter observation reveals that although DHA is incorporated preferentially into epidermal PE, this pool of phospholipid was not readily available to the epidermal phospholipases for hydrolysis and release of DHA for lipoxygenation into 17-HDoHE. It remains to be determined whether or not the epidermal phospholipases are selective for the different phospholipid pools. This attractive hypothesis is presently being explored.

METABOLISM OF POLYUNSATURATED FATTY ACIDS IN THE SKIN

The 20-carbon AA is an important PUFA in the skin. Specific enzymes from epidermis metabolize AA into a variety of oxygenated metabolites. Thus the major function of AA is to provide metabolites that regulate proliferative and differentiating processes in the skin. AA represents approximately 6–10% of the total fatty acids in the epidermal phospholipids of guinea pigs (15, 38). Similarly, human skin contains approximately 9% of AA in the epidermal phospholipids (52). Phospholipase A activity in the skin (19, 63) provides the mechanism for the release of PUFAs incorporated into epidermal phospholipids. When released, the epidermal PUFAs undergo oxidative transformations into eicosanoids via epidermal cyclooxygenase and lipoxygenase pathways.

Transformations via the Cyclooxygenase Pathway

The biosynthesis of cyclooxygenase products [prostaglandins (PGs)] from AA has been well documented in skin preparations from frogs (27), rats (62), mice (55), guinea pigs (48), and humans (23). This activity occurs primarily in the epidermis and is concentrated in the particulate microsomal fraction. The enzymes that catalyze the synthesis of PGD_2, PGE_2, and $PGF_{2\alpha}$ have all been identified in skin enzyme preparations. Furthermore, the PGE_2-9-keto reductase (the enzyme that catalyzes the transformation of PGE_2 into $PGF_{2\alpha}$) has also been described (64). A schematic representation of the cyclooxygenase pathway is shown in Figure 4.

Transformations via the Lipoxygenase Pathways

12-LIPOXYGENASE PATHWAY Interest in the possible role of lipoxygenase products in the biology of skin was sparked when it was reported that

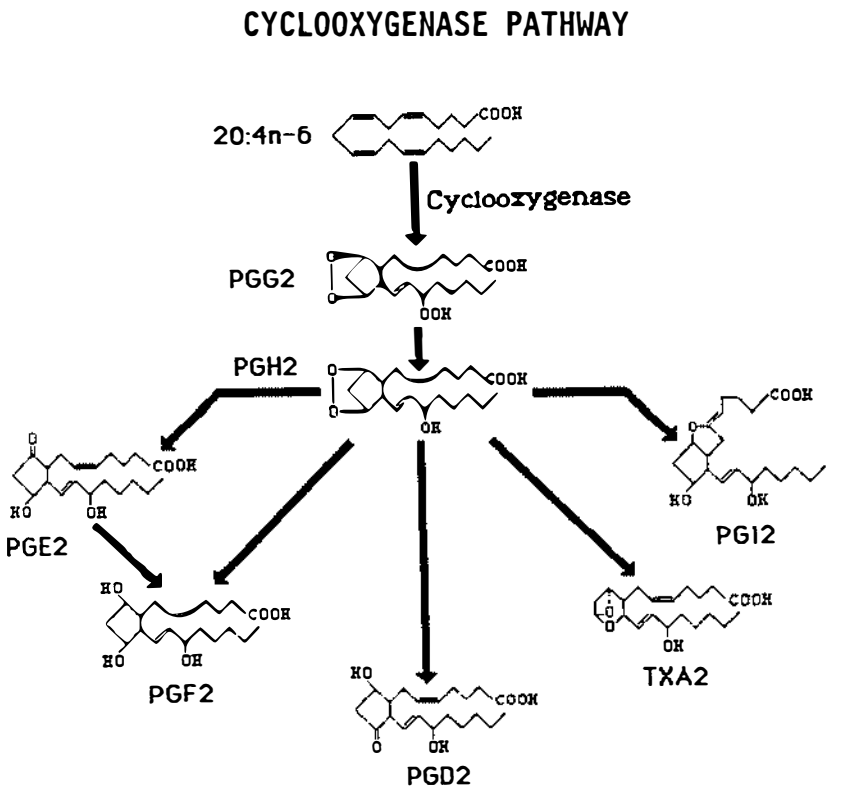

Figure 4 Metabolism of arachidonic acid via the cyclooxygenase pathway.

epidermal extracts from lesional skin of psoriatic patients (a chronic inflammatory skin disease characterized by severe scaliness, redness, and epidermal hyperproliferation) accumulated levels of 12-L-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE) that were higher than levels found in nonlesional epidermis (23). The biosynthesis of this lipoxygenase product has been reported in mouse (41, 49) and in guinea pig epidermis (48). This hydroxy fatty acid is known to be moderately proinflammatory, although its significance in epidermal biology is not fully understood. Advances in chiral phase chromatography have now revealed that the 12-HETE reported in the skin of psoriatic patients is primarily the 12(*R*) epimer and not the 12(*S*) epimer, which is the typical product of 12-lipoxygenases (56).

15-LIPOXYGENASE PATHWAY 15(*S*)-hydroxyl-5,8,11-*cis*-eicosatetraenoic acid (15-HETE) has recently been demonstrated in human skin (28), in cultured epidermal cells (keratinocytes) isolated from human neonatal foreskin (12), and in guinea pig skin (11). Interestingly, this hydroxy fatty acid has been shown to inhibit 5-lipoxygenase activity in neutrophils (51) as well as 12-lipoxygenase activity in the epidermis (29). Thus, this hydroxy fatty acid may function as an in vivo antiinflammatory metabolite of AA inflammatory metabolites.

5-LIPOXYGENASE PATHWAY The possibility that the 5-lipoxygenase pathway may be involved in cutaneous metabolism of AA was investigated in keratinocytes (60). The synthesis of lipoxygenase products by these cells was enhanced in the presence of a cyclooxygenase inhibitor indomethacin (IM), which suggests that the activity of the 5-lipoxygenase is present in these cells and with appropriate manipulation can be expressed. However, the overall 5-lipoxygenase activity in normal epidermis is negligible. Figure 5 illustrates the transformations of arachidonic acid via the lipoxygenase pathways.

MODULATION OF EPIDERMAL FATTY ACIDS AND EICOSANOIDS BY DIETARY OILS CONTAINING N-6 AND N-3 PUFAs

The excitement generated by reports of clinical improvement of patients with atopic eczema (a disease of still undefined etiology but characterized by abnormalities related to defective immune responses) after oral administration of primrose oil (34, 58) signalled a possible role of GLA and n-6-containing vegetable oils in cutaneous biology. For instance, orally administered EPO containing LIN and GLA reportedly increases tissue levels of 1-series prostaglandins and suppresses chronic inflammation (47, 65). This finding implies that GLA is elongated in vivo into DGLA and that oxidative metabolism of

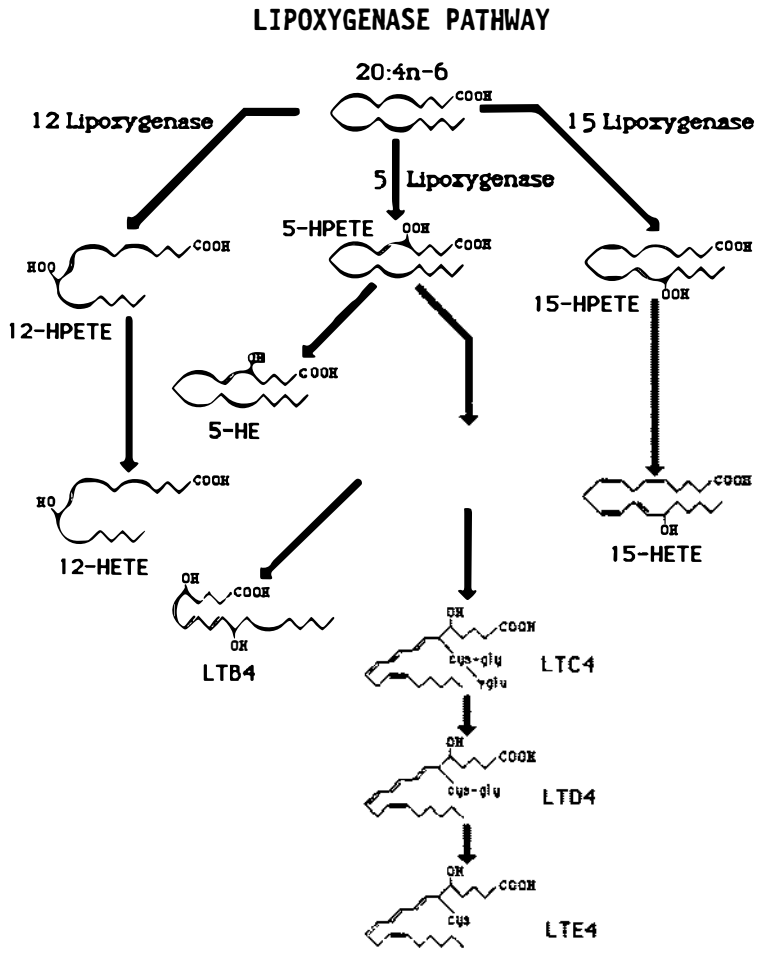

Figure 5 Metabolism of archidonic acid via the 5-, 12-, and 15-lipoxygenase pathways.

DGLA to PGs of the 1-series (PGE_1) takes place via the cyclooxygenase pathway. In some studies PGE_1 was reported to suppress the inflammations associated with adjuvant arthritis (67) and immune complex vasculitis in rats (32). Taken together, the generation of PGE_1 and its suppression of inflammation reactions seem consistent with an in vivo regulatory role by GLA-containing diets.

Similar to reports associated with dietary feeding of n-6 PUFAs, evidence that n-3 PUFAs, their cyclooxygenase products (PGs of the 3-series), and lipoxygenase products (LTs of the 5-series) can affect immune function and inflammatory reactions has aroused interest in the effects of fish oil on a

variety of chronic diseases such as hypertension (33), lupus (66), multiple sclerosis (20), rheumatoid arthritis (30), and psoriasis (31). The interest in psoriasis was accentuated by an epidemiologic study of Eskimos in Greenland by Kromann & Green (31) that revealed a 20-fold less incidence of psoriasis among the Eskimos in Greenland than in the Danish population. In psoriasis the metabolism of AA is altered and levels of proinflammatory lipoxygenase products, particularly LTB_4 (6) and 12-HETE, are elevated (23). More recently, supplementation of the diets of psoriatic patients with fish oil (containing EPA and DHA) for eight weeks (61) resulted in mild-to-moderate improvement of their psoriatic lesions. Interestingly, improved clinical response correlated with a high EPA to DHA ratio in the epidermal tissue.

To investigate possible mechanisms for the in vivo beneficial effects of the n-3 PUFAs and n-6 PUFAs, normal guinea pigs were fed diets supplemented with fish oil (rich in EPA and DHA) or borage oil (a vegetable seed oil rich in GLA). The animals whose diets were supplemented with fish oil had elevated levels of precursor EPA and DHA in epidermal phospholipids; only the level of 15-HEPE (the 15-lipoxygenase product of EPA) was elevated in the epidermis, however. Similarly, the animals whose diets were supplemented with borage oil had elevated levels of DGLA (the epidermal elongase product of GLA) in epidermal phospholipids. This increase of DGLA was accompanied by elevated tissue levels of 15-HETrE (the epidermal 15-lipoxygenase product of DGLA) as well as by increased PGE_1 (the cyclooxygenase product of DGLA).

CONCLUSIONS

Present dietary studies are consistent with the view that a diet supplemented with GLA-enriched or EPA- and DHA-enriched products can exert profound effects on endogenous epidermal fatty acid compositions as well as on its eicosanoid contents. For example, the dietary intake of a vegetable oil (borage oil) results in the uptake of GLA into epidermal phospholipids, the elongation of GLA into DGLA, and the local transformation of DGLA into PGE_1 and 15-HETrE in the epidermis of these animals by the epidermal 15-lipoxygenase. These biochemical events imply that a GLA-containing diet may provide a source for the generation of antiinflammatory metabolites endogenously. This possibility is evidenced by the increased local tissue accumulation of PGE_1 and 15-HETrE. The accumulation of these metabolites may serve as a store of endogenous antiinflammatory products that can suppress an induced local inflammation by lipoxygenase products of AA metabolism.

Similarly, the dietary intake of fish oil results in elevated tissue levels of EPA and DHA. Metabolites of EPA (15-HEPE) can be recovered from the epidermis after dietary intake of fish oil, thus indicating that EPA is metabo-

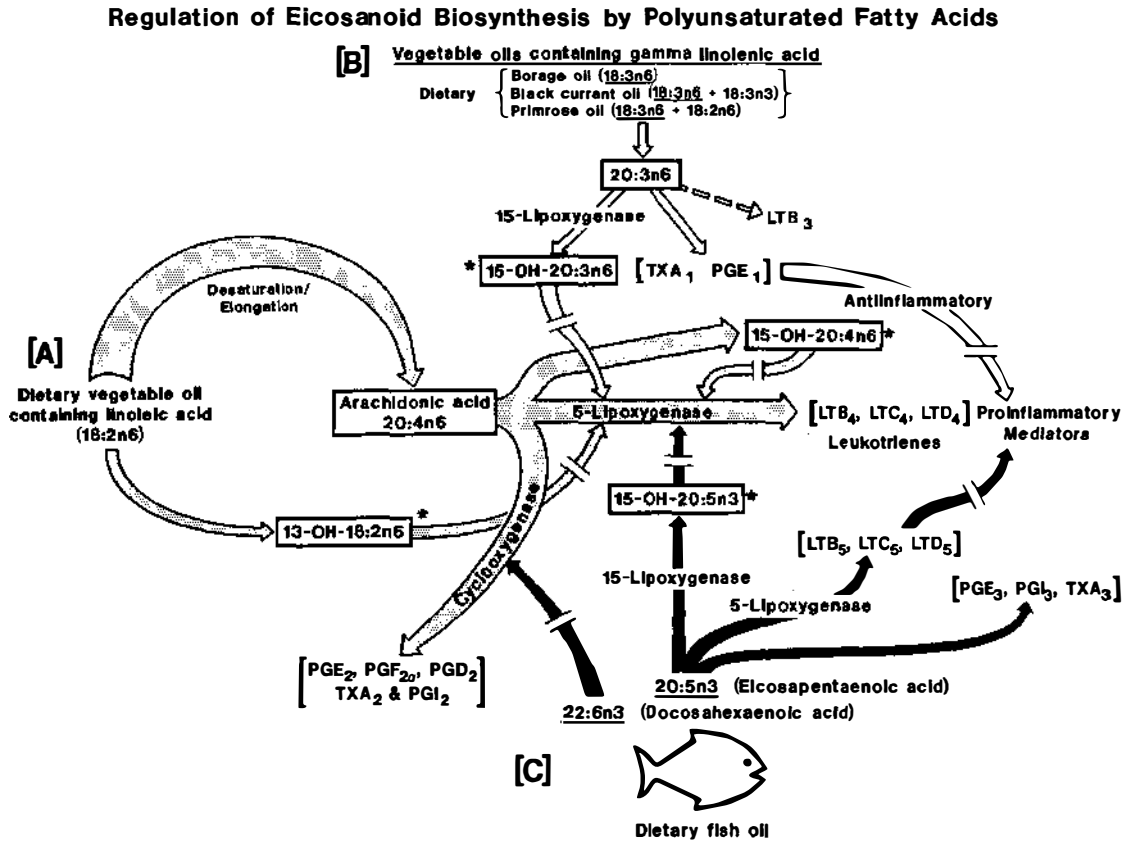

Figure 6 Speculative modulatory effects of dietary vegetable oils (*B*) and fish oil (*C*) on the 5-lipoxygenation of archidonic acid (*A*).

lized in vivo into 15-HEPE. Similarly, the metabolite of DHA (17-HDoHE) is recovered in vivo in the epidermis only after dietary feeding of high concentrates of fish oil. This observation suggests that the DHA may be incorporated into a different pool of phospholipids that is not readily released in the epidermis for metabolism into 17-HDoHE. Possibly, different phospholipases are present for different pools of phospholipids. Such a possibility warrants further investigation.

A speculative scenario of the possible modulatory effects that some of the constituent fatty acids and metabolites from vegetable and fish oils exert on the AA cascade is shown in Figure 6. The *A* pathway illustrates the consequence of dietary intake of vegetable oils such as safflower oil or olive oil, the in vivo desaturation and elongation of LIN into AA, and the 5-lipoxygenation of AA into proinflammatory leukotrienes (particularly leukotriene B_4) by polymorphonuclear cells (PMNs). The *B* pathway represents the effects 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 transformation of DGLA into 15-lipoxygenase metabolites (15-HETrE and PGE_1). The *C* pathway represents the effects of dietary intake of fish oil rich in EPA and DHA and their in vivo metabolism into respective monohydroxy acids. Metabolites from both the *B* and *C* pathways could in turn inhibit the in vivo generation of local proinflammatory leukotrienes from AA in the epidermis. These observations raise the possibility that the dietary intake of highly purified vegetable or fish oils, or the intake of the appropriate constituent PUFAs from these oils, may offer a novel and nontoxic approach to alleviating cutaneous inflammatory disorders.

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