Guinea Pig Epidermis Generates Putative Anti-Inflammatory Metabolites from Fish Oil Polyunsaturated Fatty Acids

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Clinical studies have indicated that dietary fish oil may have therapeutic value in the treatment of psoriasis, a hyperproliferative, inflammatory skin disorder characterized by elevated LTB_4. To evolve a possible mechanism for these beneficial effects, we determined the metabolic fate of fish oil derived n-3 fatty acids in the skin. Specifically, we incubated guinea pig epidermal enzyme preparations with [^{3}H]eicosapentaenoic acid (20:5n-3) and [^{14}C]docosahexaenoic acid (22:6n-3). Analyses of the radiometabolites revealed the transformation of these n-3 fatty acids into n-6 lipoxygenase (arachidonate 15-lipoxygenase) products: 15-hydroxyeicosapentaenoic acid (15-HEPE) and 17-hydroxydocosahexaenoic acid (17-HDHE), respectively. Since 15-lipoxygenase products have been suggested as possible endogenous inhibitors of 5-lipoxygenase (an enzyme which catalyzes the formation of LTB_4) we tested the ability of 15-HEPE and 17-HDHE *in vitro* to inhibit the activity of the 5-lipoxygenase. Incubations of these metabolites with enzyme preparations from rat basophilic leukemia (RBL-1) cells demonstrated that 15-HEPE (IC_{50} = 28 μM) and 17-HDHE (IC_{50} = 25 μM) are respectively potent inhibitors of RBL-I-5-lipoxygenase. The inhibitory potential of these fish oil metabolites provides a possible mechanism by which fish oil might act to decrease local cutaneous levels of LTB_4, and thereby alleviate psoriatic symptoms.
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There are reports that dietary fish oil may be beneficial, at least in part, in the treatment of psoriasis (1–3), a hyperproliferative, inflammatory skin disorder. Although the exact mechanism by which fish oil functions to ameliorate the cutaneous lesions of psoriasis has not been elucidated, there is some indication that fish oil may act by decreasing local epidermal levels of leukotriene B_4 (LTB_4), a 5-lipoxygenase product which is elevated in psoriatic epidermis (4–6). The notion that a regulation of LTB_4 synthesis may be involved is based upon increasing evidence that LTB_4 is a powerful proinflammatory agent with activities which include chemotaxis of neutrophils, augmentation of neutrophil adherence to endothelial cells and enhanced expression of C3b receptors on neutrophils (7). Leukotriene B_4 may also have a role in modulating epidermal proliferation based on its ability to stimulate DNA synthesis in keratinocytes, a primary epidermal cell type (8). *In vivo*, applications of LTB_4 to normal skin result in the induction of psoriatic-type lesions with both neutrophil infiltration (9,10) and epidermal hyperproliferation (11,12). Administration of 5-lipoxygenase inhibitors, topical or systemic, have been reported to improve the psoriatic lesions (13,14). Thus, if constituents of fish oil are transformed in the epidermis into metabolites which inhibit 5-lipoxygenase activity and LTB_4 synthesis, this may explain, at least in part, how fish oil alleviates psoriatic symptoms.

The epidermis is capable of converting plant-derived n-6 fatty acids into 15-lipoxygenase products (n-6 hydroxy fatty acids) (15,16). These hydroxy fatty acids have been shown to inhibit LTB_4 synthesis (16–18). The most abundant 15-lipoxygenase products in guinea pig epidermis are 13-hydroxyoctadecadienoic acid (13-HODE), a product of linoleic acid (18:2n-6), and 15-hydroxyeicosatetraenoic acid (15-HETE), a product of arachidonic acid (20:4n-6) (19). However, unlike the n-6 fatty acids, the metabolic fate of fish oil-derived fatty acids in the epidermis is unknown. Fish oils contain low levels of n-6 fatty acids but are rich in the n-3 polyunsaturated fatty acids (PUFAs) — eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3) (20). We reasoned that it is possible that 20:5n-3 and 22:6n-3, like the n-6 fatty acids, are transformed in the epidermis into 15-lipoxygenase products, and that these products could inhibit local LTB_4 synthesis. To investigate this hypothesis, we examined the metabolic fates of 20:5n-3 and 22:6n-3 by incubating them with guinea pig epidermal preparations. The metabolites were identified and then tested for their abilities to inhibit the biosynthesis of LTB_4 generated by RBL-I (rat basophilic leukemia) cells.

MATERIALS AND METHODS

[1-^{14}C]18:2n-6 (Spec. act. = 55.6 mCi/mmol), [1-^{14}C]20:4n-6 (Spec. act. = 54.9 mCi/mmol), [1-^{14}C]22:6n-3 (Spec. act. = 56.9 mCi/mmol) and [^{3}H]20:5n-3 (Spec. act. = 79.0 Ci/mmol) were purchased from DuPont, NEN Products Division (Boston, MA). Unlabelled fatty acids were purchased from NuChek Prep (Elysian, MN). 13-HODE, 15-HETrE, 15-HETE, 12-HEPE and 15-HEPE were purchased from Cayman Chemical (Ann Arbor, MI). Reduced glutathione (GSH) was purchased from Boehringer Mannheim (Indianapolis, IN), $CaCl_2$ was purchased from JT Baker Chemical Co. (Phillipsburg, PA) and *N,O-bis*(trimethylsilyl)trifluorocetamide (BSTFA) was purchased from Supelco, Inc. (Bellfonte, PA). All solvents were of HPLC quality and were purchased from Fisher Scientific Co (Fair Lawn, NJ).

Preparation of epidermal homogenates and incubations with 20:5n-3 and 22:6n-3. Incubations with guinea pig epidermal homogenates were conducted to determine the metabolic fate of 20:5n-3 and 22:6n-3 in the epidermis. Hair from the dorsum of male Hartley guinea pigs (400–450 g; Simonsen) was removed by shaving

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Abbreviations: PUFA, polyunsaturated fatty acid; LTB_4, leukotriene B_4; HODE, hydroxyoctadecadienoic acid; HETrE, hydroxyeicosatrienoic acid; HETE, hydroxyeicosatetraenoic acid; HEPE, hydroxyeicosapentaenoic acid; HDHE, hydroxydocosahexaenoic acid; GC/MS, gas chromatography/mass spectrometry; RP-HPLC, reverse phase-high performance liquid chromatography; GSH, reduced glutathione; BSTFA, *N,O-bis*(trimethylsilyl) trifluoroacetaminde

and depilation with sodium thioglycollate (Nair, Carter-Wallace, Inc., New York, NY) followed by rinsing with deionized water. The animals were sacrificed by cervical dislocation and the skin was rapidly removed. Superficial 0.2 mm slices were then removed by keratome (Storz, St. Louis, MO); histologic evaluation showed these keratome slices to be >85% epidermis. These epidermal slices were promptly placed in ice-cold buffer (50 mM phosphate, pH 7.4, 1 mM EDTA) and were homogenized with a Polytron (Brinkmann Instruments, Westbury, NY). This crude epidermal homogenate was centrifuged at 10,000 g for 20 min at 4°C to obtain a supernatant containing a mixture of particulate and cytosolic (incl. lipoxygenase) enzymes. The 10,000 g supernatant was used for incubations. A typical incubation consisted of 10 mg protein diluted in 2 mls buffer with GSH (1.0 mM). After pre-incubation at 37°C for 10 min, the fatty acid substrate was added (20 μM, 0.2 μCi/incubation) and the mixture incubated at 37°C for 20 min. The incubation was terminated by placement of the tube in ice and immediate acidification to pH 3.0. The incubation products were extracted with $CHCl_3$/MeOH (2:1, v/v).

Generation and identification of epidermal lipoxygenase metabolites from 20:5n-3 and 22:6n-3. The extracted radiometabolites of incubations of [^{3}H]20:5n-3 and [^{14}C]22:6n-3 with the epidermal 10,000 g supernatant were analyzed by chromatographic co-migration with radiolabelled hydroxy fatty acid standards. Soybean lipoxidase was used to convert 20:5n-3 and 22:6n-3 to the reference 15-lipoxygenase products, 15-HEPE and 17-HDHE, respectively, as previously reported (21). Similarly, human platelet preparations were used to convert 20:5n-3 and 22:6n-3 to the reference 12-lipoxygenase products, 12-HEPE (22,23); 14-HDHE and 11-HDHE (24), respectively. Identities of these reference metabolites were confirmed by GC/mass spectrometry. Analysis of each of the epidermal radiometabolites was performed by using two reverse phase-high performance liquid chromatography (RP-HPLC) systems with a Beckman 5um Ultrasphere ODS column (25 cm × 4-6 mm id), Beckman model 100A/100A pumps, and a Radiomatic HS Flo-one on-line radioactive flow detector. RP-HPLC system I utilized a solvent-system of methanol and H_2O (acidified to pH 3.0 with acetic acid) (25). This system was run at a flow rate of 1.0 ml/min in a stepwise gradient with 74% methanol from 0-55 min. For additional confirmation, the metabolites were chromatographed on RP-HPLC system II utilizing a solvent system of acetonitrile and water (0.02% H_3PO_3) modified from Van Rollins *et al.* (26). This second system was run at a flow rate at 20.0 ml/min at 50% acetonitrile from 0-30 min and 100% acetonitrile from 30-45 min. Co-migration of the metabolites with authentic samples in both systems was considered a base for purity.

For additional confirmation of identity, the epidermal metabolite of 20:5n-3 was subjected to gas chromatography/mass spectrometry (GC/MS). Specifically, that fraction of the eluate corresponding with 15-HEPE was collected by a Pharmacia FMC 100 fraction collector (Pharmacia Biochemicals, Piscataway, NJ) and treated with fresh methanolic ethereal diazomethane and BSTFA to form the fatty acid methyl ester, trimethylsilyl ether derivative (27). Authentic 15-HEPE was similarly derivatized. These derivatives were analyzed by GC/MS using an HP5790 gas chromatograph (Hewlett-Packard, Palo Alto, CA) equipped with a 15 m DB-1 fused silica column (J & W Scientific, Rancho Cordova, CA), interfaced with a VG ZAB-HS-ZF mass spectrometer (VG Analytical, Wythenshawe, England), as previously described (16). The oven was operated with a thermal gradient beginning at 220°C increasing 4°C; the MS was in electron impact (EI) mode at 70 mV. The fragment ions from the derivatized epidermal metabolite corresponds with those of the derivatized authentic 15-HEPE and those reported by Mitchell *et al.* (29) and Takenaga *et al.* (23). The prominent ions (*M/Z*) and mode of origin of the derivatized epidermal metabolite were: 404(M), 389(M-15, loss of CH_3), 373 (M-31, loss of OCH_3), 335(M-69, loss of C_5H_9, indicating an n-3 fatty acid), 245(335-90, loss of TMSOH), and 173 ($C_5H_9CHOTMS$, indicating hydroxylation at the n-6 position). The inability to obtain authentic sample for 17-HDHE for comparison prevented us from obtaining a satisfactory GC/MS profile of the epidermal metabolite of 22:6n-3 (17-HDHE). Identity of the epidermal metabolite of 22:6n-3 was therefore limited to chromatography on two RP-HPLC systems and on UV spectra.

Generation of 15-HEPE and 17-HDHE by soybean lipoxidase. Samples of 15-HEPE and 17-HDHE were synthesized by incubating the precursor fatty acids (20:5n-3 and 22:6n-3) with soybean lipoxidase (23) (Sigma Chemical Co., St. Louis, MO), followed by reduction of the intermediate hydroperoxides with triphenylphosphine and purifying the resultant hydroxy fatty acids by HPLC (21). The identities of these two soybean lipoxidase hydroxy fatty acids were confirmed by RP-HPLC and GC/MS, as previously published. Quantification was achieved by integrated optical density at 237 nm against an authentic standard of 15-hydroxyeicosatrienoic acid (15-HETrE). The HPLC and GC/MS characterized metabolites of soybean lipoxidase served as authentic references for the generated epidermal lipoxygenase products.

Effects of generated epidermal 15-HEPE and 17-HDHE on the activity of TBL-1 5-lipoxygenase pathway. The finding that the epidermal lipoxygenase products of 20:5n-3 and 22:6n-3 are 15-hydroxyeicosapentaenoic acid (15-HEPE) and 17-hydroxydocosahexaenoic acid (17-HDHE) led us to investigate whether these hydroxy fatty acids could modulate the synthesis of LTB_4 (a 5-lipoxygenase product of 20:4n-6). To evaluate the effects of epidermal 15-hydroxyeicosapentaenoic acid (15-HEPE) and 17-hydroxydocosahexaenoic acid (17-HDHE) on the biosynthesis of leukotriene B_4 (LTB_4) we used the *in vitro* model of RBL-1 cell homogenate (an effective system for evaluating the effects of chemical agents on 5-lipoxygenase pathway (16). Specifically, RBL-1 cells were placed in buffer (50 mM phosphate, pH 7.4, 1 mM EDTA) at a concentration of 3×10^7 cells/ml and then homogenized by sonication. This crude homogenate was centrifuged at 10,000 g to obtain the supernatant which contained the 5-lipoxygenase activity. The supernatant enzyme preparations were pre-incubated at 37°C for 10 min with 2 mM $CaCl_2$ and varying concentrations (0-50 μM) of either 15-HEPE

or 17-HDHE. The reaction was initiated by the addition of [^{14}C]20:4n-6 (20 μM; 0.2 μCi) to each respective incubation mixture. After 20 min at 37°C, the incubations were terminated by placement of tubes in ice, followed by acidification to pH 3.0. The incubation products were extracted with $CHCl_3$/MeOH (2:1, v/v). Conversion of 20:4n-6 into 5-lipoxygenase products (mainly 5-HETE and LTB_4) by RBL-1 supernatant was determined by a reverse phase-HPLC system using a solvent system of methanol/water (0.08% HOAc, pH 6.2) modified from Henke *et al.* (28). This system was run at a constant flow rate of 1.4 ml/min with an increasing gradient of methanol as follows: 55% methanol from 0–20 min, 66% from 20–40 min, 77% from 40–60 min, and 100% from 60–75 min. Similarly, we tested the effects of the generated epidermal metabolites of n-6 fatty acids, such as the 15-lipoxygenase products of arachidonic acid, (15-HETE) and linoleic acid, 13-hydroxyoctadecadienoic acid (13-HODE) in order to compare their inhibitory potentials with those of the n-3 fatty acids.

RESULTS

Identification of epidermal lipoxygenase products of 20:5n-3 and 22:6n-3. Analysis of the radiometabolites of [^{3}H]20:5n-3 (20 μM) and [^{14}C]22:6n-3 (20 μM) from incubations with the epidermal 10,000 g supernatant showed conversion predominantly into the 15-lipoxygenase products: [^{3}H]15-HEPE and [^{14}C]17-HDHE, respectively. Using two RP-HPLC systems, the identities of the epidermal metabolites of [^{3}H]20:5n-3 and [^{14}C]22:6n-3 were shown to have chromatographic profiles similar to the radiolabelled hydroxy fatty acid standards of the soybean lipoxidase products of 20:5n-3 and 22:6n-3. A typical profile of the separation of the epidermal lipoxygenase products of 20:5n-3 and 22:6n-3 in the solvent system I is shown in Figure 1A. This Figure shows that the major epidermal metabolite of 20:5n-3 co-chromatographs with the 15-lipoxygenase product, 15-HEPE when using the methanol-based RP-HPLC system described above. Figure 1B similarly shows that the major epidermal metabolite of [^{14}C]22:6n-3 co-chromatographs with the 15-lipoxygenase product, 17-HDHE. Co-migration of these two epidermal hydroxy metabolites with soybean lipoxidase products was similarly established using a second solvent system II —acetonitrile-based RP-HPLC system. Additionally, the identity of the epidermal metabolite of 20:5n-3, and not 22:6n-3, was confirmed by comparing the mass spectrometry profiles from the fatty acid methyl ester/trimethylsilyl (TMS) ether derivatives of this metabolite and authentic 15-HEPE as described under Methods.

Comparative metabolic transformations of n-3 and n-6 polyunsaturated fatty acid into monohydroxy acids by guinea pig epidermal homogenates. In these experiments, the incubations of the two n-3 PUFAs 22:6n-3 and 20:5n-3 with epidermal homogenates at a similar concentration (20 μM) and time (20 min) revealed that 30.4 ± 1.0% of 22:6n-3 was converted into 17-HDHE, whereas only 17.8 ± 1.4% of 20:5n-3 was converted into 15-HEPE (Fig. 2). On the other hand, similar incubations with 18:2n-6 and 20:4n-6 revealed that the two n-6 PUFAs were less readily converted to their corresponding 15-lipoxygenase products when compared to the n-3 fatty acids. For instance, 15.7 ± 0.5% of 20:4n-6 was converted into 15-HETE, whereas only 4.0 ± of 18:2n-6 was converted into 13-HODE.

Inhibition of RBL-1 cell 5-lipoxygenase activity by guinea pig generated 15-HEPE and 17-HDHE. Incubations of RBL-1 cell homogenates with generated guinea pig 15-HEPE and 17-HDHE revealed that both monohydroxy fatty acids are potent inhibitors of 20:4n-6 transformation into LTB_4 and 5-HETE, the two major metabolites of 20:4n-6 by RBL-1 homogenate (Fig. 3). The inhibitory effects are dose dependent (0–50 μM). Since the major metabolites of 20:4n-6 by the RBL-1 homogenate are LTB_4 and 5-HETE, the inhibitory effects of both 15-HEPE and 17-HDHE are on the common 5-lipoxygenase pathway. The determined IC_{50} of 15-HEPE and 17-HDHE were 28 μM and 25 μM, respectively. For comparison, the determined IC_{50} of 15-HETE (the epidermal 15-lipoxygenase product of 20:4n-6) and the IC_{50} of 13-HODE (the 15-lipoxygenase product of linoleic acid) were 37 μM and >50 μM, respectively. Taken together, the ability of the epidermal 15-lipoxygenase products to inhibit 5-lipoxygenase follows the order 17-HDHE≥15-HEPE≥-HETE>>13-HODE.

DISCUSSION

Fish oil has been reported to be beneficial in the treatment of psoriasis (1–3), a hyperproliferative, inflammatory skin disorder which is associated with elevated levels of LTB_4, a 5-lipoxygenase product (4–6). To elucidate a possible mechanism of these beneficial effects we investigated whether the major PUFA constituents of fish oil, 20:5n-3 and 22:6n-3, can be transformed by epidermal preparations into metabolites which inhibit LTB_4 synthesis. Our data indicate: i) that both 20:5n-3 and 22:6n-3 are readily converted by epidermal 15-lipoxygenase into 15-HEPE and 17-HDHE, and ii) that both 15-HEPE and 17-HDHE are potent inhibitors of RBL-1 5-lipoxygenase activity. Specifically, incubations of guinea pig epidermal enzyme preparations with [^{3}H]20:5n-3 and [^{14}C]22:6n-3 resulted in the formation of radiometabolites which were chromatographically similar to the 15-lipoxygenase products, 15-HEPE and 17-HDHE, respectively (Fig. 1). Similar incubations with 18:2n-6 and 20:4n-6 (16) showed that these PUFAs are also converted to their corresponding 15-lipoxygenase products — 13-HODE and 15-HETE, respectively. A comparison of the relative utilization of the above four n-3 and n-6 polyunsaturated fatty acids at the same concentration and time showed preferential metabolism of the fatty acid substrates by the guinea pig epidermal 15-lipoxygenase as follows: 22:6n-3>20:5n-3>20:4n-6>18:2n-6 (Fig. 2). The finding that guinea pig epidermal homogenates convert n-3 fatty acids to 15-lipoxygenase products is consistent with the ability of human epidermal homogenates to transform 20:5n-3 to 15-HEPE (30). These results add to other similarities which exist in polyunsaturated fatty acid metabolism in the epidermis of these species (31,32).

Since 20:5n-3 and 22:6n-3 are readily converted to epidermal 15-lipoxygenase products, and since 15-

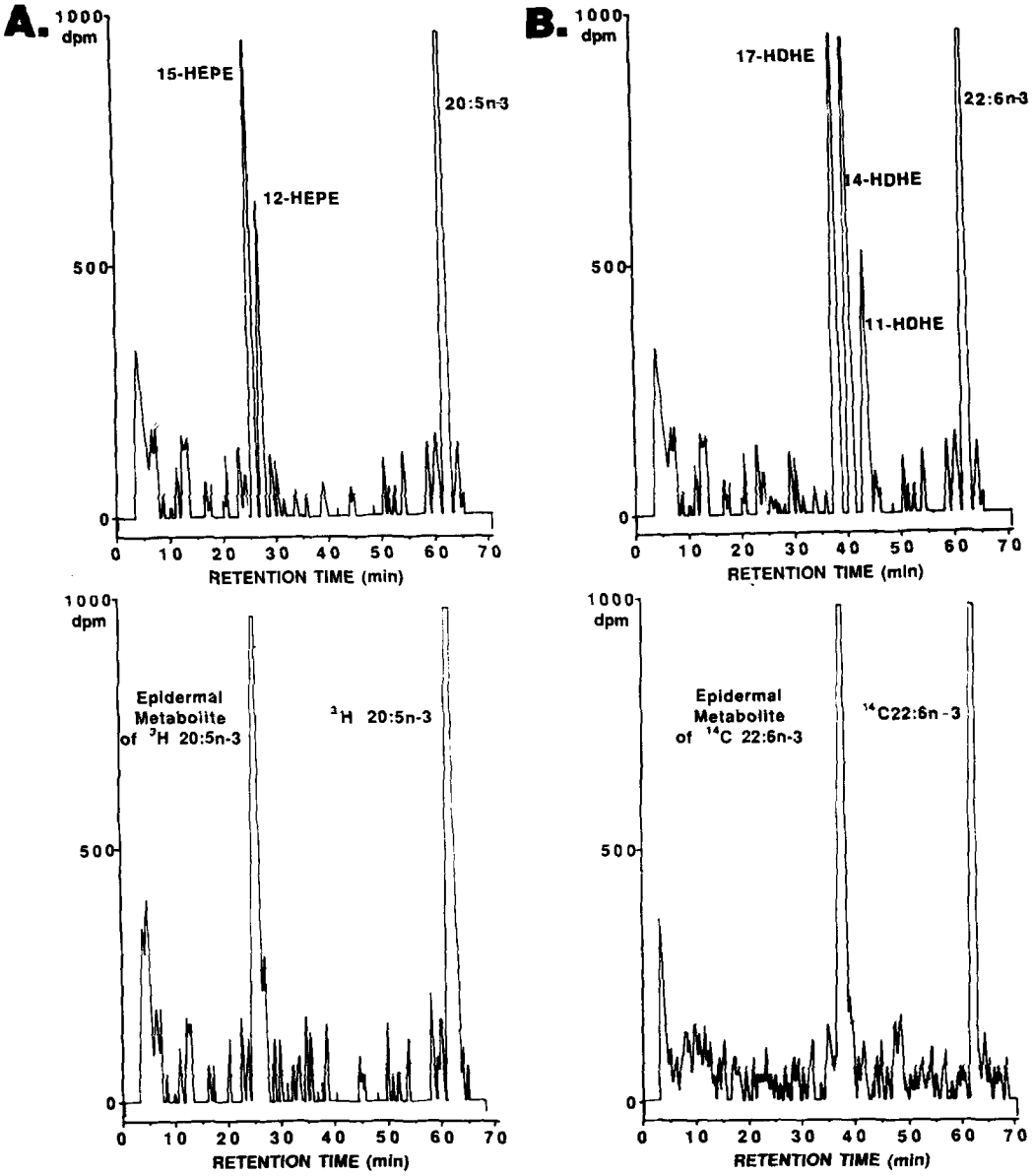

FIG. 1. RP-HPLC radiochromatograms of lipoxygenase products of n-3 fatty acids using solvent system I of 74% MeOH in H_2O acidified to pH 3.0 with HOAc, as described in the text. A) Above: Reference lipoxygenase metabolites of [^{3}H]20:5n-3 from soybean lipoxidase (15-HEPE, TR = 25.8) and human platelets (12-HEPE, RT = 28.0). Below: Lipids extracted from incubations of [^{3}H]20:5n-3 (20 μM) with guinea pig epidermal homogenates (RT = 25.6). B) Above: Reference lipoxygenase metabolites of [^{14}C]22:6n-3 from soybean lipoxidase (17-HDHE, RT = 38.3) and human platelets (14-HDHE and 11-HDHE, RT = 41.0 and 43.9). Below: Lipids extracted from incubations of [^{14}C]22:6n-3 (20 μM) with guinea pig epidermal homogenates (RT = 38.3).

lipoxygenase products have been reported to inhibit LTB_4 synthesis (17,18), we tested the ability of 15-HEPE and 17-HDHE to inhibit 5-lipoxygenase activity using an *in vitro* model of RBL-1 5-lipoxygenase. Our data demonstrated that 15-HEPE and 17-HDHE are both potent inhibitors of the RBL-1 5-lipoxygenase (*Fig. 3*). 15-HEPE inhibited 5-lipoxygenase with an IC_{50} of 28 μM, whereas 17-HDHE inhibited with an IC_{50} of 25 μM. The n-6 fatty acid derived 15-lipoxygenase products 15-HETE and 13-HODE were less potent inhibitors; 15-HETE inhibited with an IC_{50} of 37 μM while 13-HODE inhibited with an IC_{50} of >50 μM. The inhibition data for the 5-lipoxygenase in our RBL-1 homogenate system shows qualitative agreement with similar studies with intact neutrophils in which 15-HETE and 13-HODE inhibited 5-lipoxygenase with IC_{50} of 8 μM and 32 μM, respectively (18). Therefore, our results support the hypothesis that 20:5n-3 and 22:6n-3, the major constituents of fish oil, are converted by the epidermis to 15-lipoxygenase products (15-HEPE and 17-HDHE), and that these epidermal metabolites may increase the overall levels of en-

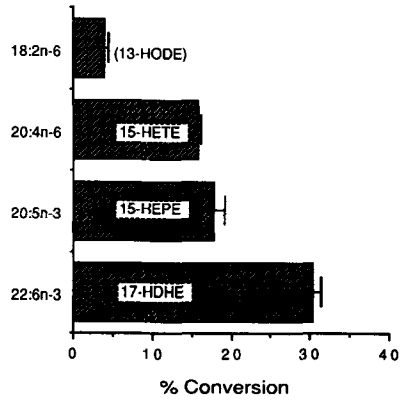

FIG. 2. Comparative metabolic transformations of n-3 and n-6 fatty acids (20 μM) into 15-lipoxygenase products by guinea pig epidermal homogenates. Details of respective incubations are contained in the text. Each value represents the mean ± SEM of three separate experiments.

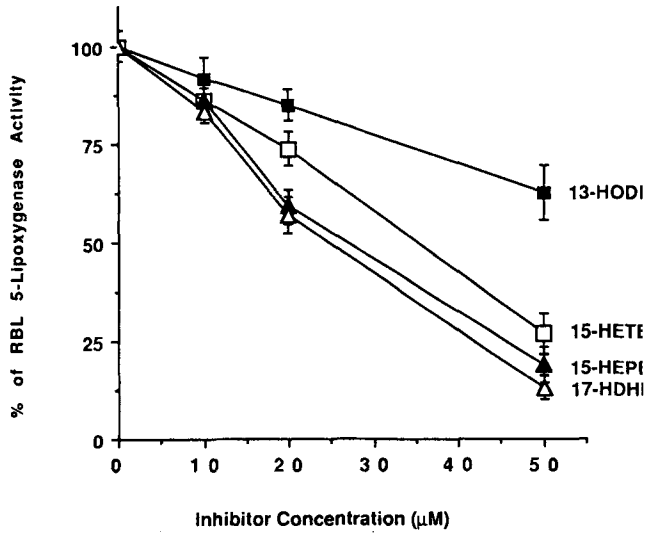

FIG. 3. Inhibitory effects of: 13-HODE (■), 15-HETE (□), 15-HEPE (▲), and 17-HDHE (△) on the activity of 5-lipoxygenase from RBL-1 cell homogenates. Each point represents the mean ± SEM of three experiments. Approximate IC_{50} values in μM for 13-HODE, 15-HETE, 15-HEPE, and 17-HDHE are >50, 37, 28 and 25, respectively.

dogenous inhibitors of 5-lipoxygenase in the skin. Such a possibility was recently demonstrated in the epidermis of guinea pigs fed fish oil rich in 20:5n-3 and 22:6n-3 PUFAs (33). This implies that dietary fish oil may lead to a decrease in local LTB_4 synthesis by neutrophils which are known to infiltrate the epidermis in lesions of psoriasis.

Interestingly, there is precedence to support the above hypothesis with fish oil. In humans, dietary vegetable oils rich in γ-linolenic acid (18:3n-6) have been reported to alleviate the inflammatory skin lesions associated with atopic eczema (34,35), a condition which is also characterized by elevated lesional LTB_4 (36). In guinea pigs, dietary supplementation with 18:3n-6 results in significantly elevated epidermal levels of 18:3n-6, its elongase product dihomo-γ-linolenic acid (20:3n-6), and the latter's 15-lipoxygenase product 15-hydroxyeicosatrienoic acid (15-HETrE). Since 15-HETrE is a potent inhibitor of 5-lipoxygenase activity (16,17), it has been suggested that the beneficial effects of oils rich in 18:3n-6 on atopic eczema may result from an inhibition of lesional LTB_4 synthesis (16, 37).

The synthesis of 15-lipoxygenase products *in vivo* depends on the incorporation of the dietary fatty acids into the epidermal phospholipids and their subsequent release prior to transformation into hydroxy fatty acids by the epidermal 15-lipoxygenase. Neutrophils and platelets, for instance, readily incorporate 20:5n-3 and 22:6n-3 into phospholipids. However, when these cells are stimulated by appropriate agonists, there is negligible release of 22:6n-3 when compared to 20:5n-3 (38). Similarly, epidermis may favor the release of 20:5n-3 over 22:6n-3. Recent data from our laboratory does indicate that although both 20:5n-3 and 22:6n-3 are incorporated into the epidermal phospholipids of guinea pigs fed fish oil diets, the *in vivo* epidermal level of 15-HEPE is markedly greater than that of 17-HDHE (33), suggesting a possible impaired hydrolysis and release of free 22:6n-3 from the epidermal phospholipids. This possibility may explain why clinical improvement of psoriatic patients whose diets were supplemented with fish oil correlated with patients with elevated epidermal ratios of 20:5n-3/22:6n-3 (1).

The conversion of n-3 and n-6 polyunsaturated fatty acids contained in certain dietary oils to 15-lipoxygenase products which can inhibit LTB_4 synthesis provides an attractive mechanism by which these oils may exert beneficial effects on inflammatory, hyperproliferative skin disorders. It is, however, premature to suggest that the beneficial effects of fish oil on psoriasis is limited to or dependent upon this mechanism alone. In fact, 20:5n-3 has been reported to directly inhibit the conversion of 20:4n-6 to LTB_4 in neutrophils (39,40), presumably acting as a substrate competitor. Nonetheless, our studies strongly suggest that the role of epidermal 15-lipoxygenase in generating local putative antiinflammatory hydroxy acids may prove to be more important in modulating local generation of LTB_4 by neutrophils which infiltrate the epidermis. This possibility underscores the need for further investigation into the role of fish oil-derived 15-lipoxygenase products in other hyperproliferative and inflammatory skin disorders.

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