Psoriasis is a common chronic inflammatory and proliferative skin disease characterised by epidermal neutrophil infiltration which may be induced by chemotactic substances in the involved epidermis. Superficial psoriatic scale was shown to contain biologically active amounts of leukotriene B₄ and monohydroxy-eicosatetraenoic acid (HETE)-like material as determined by assay for chemokinetic activity in high performance liquid chromatography (HPLC) fractions of scale extracts. Extracts of scale and chamber fluid from abraded lesional and uninvolved psoriatic skin were purified by HPLC and appropriate fractions were analysed by gas chromatography - mass spectrometry (GC-MS). The following monohydroxy metabolites of arachidonic, linoleic and 11,14-eicosadienoic acids were identified: 15-HETE, 12-HETE, 11-HETE, 9-HETE, 8-HETE, 5-HETE, 13-hydroxy-octadecadienoic acid (13-HODD), 9-HODD and 15-hydroxy-eicosadienoic acid (15-HEDE). The results suggested that 12-HETE, 13-HODD and 9-HODD are the most abundant monohydroxy fatty acids in the psoriatic skin extracts described above. Assays of 13-HODD, 9-HODD and 15-HEDE for chemokinetic activity were negative with concentrations up to 10⁻⁴M. The biological significance of these three compounds in not known, but some of the hydroxylated metabolites of arachidonic acid may, by virtue of their chemotactic properties, be relevant to the pathogenesis of the psoriatic neutrophil infiltrate.

INTRODUCTION

Since 1967 the in vitro biosynthesis by mammalian lipoxygenases of various monohydroxy metabolites of arachidonic (1-4), linoleic (5-8) and 11,14-eicosadienoic (7) acids, and of the arachidonate metabolite, leukotriene B₄ (3), has been reported. Leukotriene B₄ is one of the most potent leukocyte chemokinetic and chemotactic compounds known (9,10). Most of the monohydroxy metabolites of arachidonic acid also have chemokinetic and chemotactic properties although they are much less potent than leukotriene B₄ (4, 11-13). There are, with one exception (14), no conclusive reports of the in vivo production of the monohydroxy compounds in human subjects and few conclusive reports of the in vivo production of leukotriene B₄ (15-17). Thus their pathophysiological significance is uncertain.

Psoriasis is a common chronic inflammatory skin disease characterised
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by epidermal proliferation and neutrophil infiltration which is reported to be one of the first events in the evolution of the skin lesion (18). The release of biologically active amounts of leukotriene B4 and monoHETE-like material into skin chamber fluid from abraded psoriatic skin lesions has recently been reported by us (15). The present study shows that biologically active amounts of leukotriene B4 and monoHETE-like material are also present in the superficial scale of psoriatic skin lesions. The identification of mono-hydroxy fatty acid compounds in psoriatic skin is reported, and semiquantitative data comparing levels in chamber fluid from lesional and uninvolved skin are also presented.

METHODS

Materials

Sodium borohydride, arachidonic, linoleic and 11,14-eicosadienoic acids were obtained from Sigma London, Poole, England. Ethyl acetate, hexane, diethyl ether, propan-2-ol, acetic acid (all HPLC grade) and Dextran 70 Injection B.P. (6% w/v dextran in 0.9% NaCl) were obtained from Pisons, Loughborough, England. Methanol, n-heptane and 1,2-dichloroethane (all AnalaR grade) were obtained from B.D.H., Poole, England. The methanol and n-heptane were distilled in glass before use. Diazomethane was prepared from 'Diazald' (Aldrich, Gillingham, England). Bis(trimethylsilyl)trifluoroacetamide (BSTFA) was obtained from Pierce and Warriner, Chester, England; Eagle's minimal essential medium and 1.0M HEPES buffer from Wellcome, Beckenham, England; Heparin Injection B.P. (5000 u/ml) from Paines and Byrne, Greenford, England; Agarose-Indubiose from L'Industrie Biologique Francais, Clichy, France; and Lipidex 5000 from Packard, Caversham, England. All other reagents were obtained from B.D.H.

Synthesis of authentic hydroxy fatty acids

Leukotriene B4 (5S,12R-dihydroxy-6,14-cis-8,10-trans-eicosatetraenoic acid, LTB4) was biosynthesised as previously described (19) and was finally purified by straight phase HPLC to remove the 5S,12S-6,10-trans-8,14-cis isomer of LTB4 (20).

Monohydroxy fatty acids were synthesised by a modification of a described photo-oxidation method (21). Arachidonic acid, linoleic acid (100 mg each), 11,14-eicosadienoic acid (35 mg) and [1-14C]arachidonic acid (10 μCi, 191 μCi/mg) were dissolved in separate solutions (10 ml) of methylene blue in methanol (0.1% w/v). Photolysis was carried out by irradiating each solution with 3 500 watt Phillips PF 318 P2/3 bulbs at a distance of approximately 30 cm. A stream of oxygen was bubbled through the solution and the reaction was kept cool (less than 10°C) by circulating cold water in a water jacket. Preliminary experiments with arachidonic acid showed that the optimum yield of mono-oxygenated products occurred after approximately 2½ hours of irradiation. At this time the solution was evaporated under reduced pressure almost to dryness. Ice cold water was then added and
the pH adjusted to 3.5 with 0.05M HCl. The oxygenated products were extracted twice into equal volumes of diethyl ether, the methylene blue remaining in the aqueous phase. This organic phase was then evaporated under reduced pressure almost to dryness and 10 ml 0.05M borate-HCl buffer, pH 9.0, was added. The hydroperoxides present were then reduced to the hydroxides by the addition of sodium borohydride (50 mg) in 2-3 ml ethanol. This reduction was carried out at 4°C for 30 min followed by a further 45 min at room temperature. The solution was then acidified to pH 3.5 with 4M HCl and the hydroxides were extracted into two equal volumes of diethyl ether. The organic phase was dried under reduced pressure.

The products obtained were subjected to preliminary purification by reversed phase gel partition chromatography on Lipidex 5000 (100 ml bed volume) using a solvent system consisting of methanol/water/1,2-dichloroethane/acetic acid (750:150:150:1, by vol.). The column effluent was monitored for ultraviolet absorbance at 250 nm and was collected in 5 ml fractions. Where radioactive substrate was used aliquots from these fractions were subjected to scintillation counting. Fig. 1 shows the radioprofile of reduced products following photo-oxidation of [1-14C] arachidonic acid. Peak B contained a

![Graph](https://example.com/graph.png)

Fig. 1 Elution of [1-14C] Arachidonic Acid Photo-Oxidation Products on Reversed Phase Gel Partition Chromatography (Lipidex 5000).
mixture of monohydroxy fatty acids and peak A further oxygenated products. Peaks comparable to A and B were obtained when effluent was monitored for ultraviolet absorbance. Fractions forming peak B were pooled and evaporated and the positional isomers were separated by straight phase HPLC. This was carried out using a semi-preparative Spherisorb SSW silica column (25 cm x 8 mm i.d.) eluted with hexane/propan-2-ol/methanol/acetic acid (975:22:26:1, by vol.) at a flow rate of 2.7 ml/min. The ultraviolet absorbance of the effluent was monitored at 235 nm and only hydroxy fatty acids containing the conjugated diene chromophore were detected.

Photo-oxidation of arachidonic and linoleic acids yielded the hydroxy fatty acids listed in Table 1. Following HPLC purification, gas chromatographic analysis showed that the purified 15-HETE was only partly separated from 14-HETE (which lacks the chromophore and is thus undetectable by HPLC with ultraviolet absorbance detection at 235 nm). The purified 13-HODE solution contained approximately 20% 12-HODE. All other hydroxy fatty acids appeared chromatographically pure.

Following HPLC purification of photo-oxidised 11,14-eicosadienoic acid, gas chromatographic analysis showed that 15-HEDE was not separated from 14-HEDE, which was present in equivalent amounts. Further purification of 15-HEDE by straight phase HPLC using a less polar solvent system comprising hexane/propan-2-ol/methanol/acetic acid (1070:5:15:1, by vol.) gave a final 15-HEDE sample that was 75% pure on gas chromatography.

Recovery and extraction of scale and chamber fluid samples

Samples were obtained from the skin of psoriatic patients who had given informed consent. The project was approved by the Institute Ethical Committee. The untreated lesional and uninvolved skin of four patients was abraded with a scalpel blade until a glistening surface with minimal punctate bleeding was obtained. Histological examination of abraded lesional skin showed that most or all of the suprapapillary epidermis had been removed while most of the deeper epidermis remained intact. Cylindrical plastic chambers (3.5 cm²) were fixed to the abraded sites with cyanoacrylate glue. One ml sterile phosphate buffered saline (0.04M sodium phosphate, 0.154M NaCl, pH 7.3) was added to each chamber and was removed after 35 min. Four chambers were affixed to each patient, yielding 2 ml pooled fluid from lesional and uninvolved skin in each case. To each sample was added an equal volume of 0.1M sodium acetate buffer, pH 3.5, and this mixture was partitioned twice with 2 volumes ethyl acetate. The evaporated ethyl acetate residue was partitioned between 4 ml n-heptane and 3 ml methanol to remove non-polar material. The methanol phase was collected and evaporated and the residue was subjected to straight phase HPLC as described below.

Samples of psoriatic scale (55 - 150 mg wet weight) were carefully
obtained by gentle abrasion of skin lesions. Each sample was vortexed with a mixture of 6 ml each of 0.1M sodium acetate buffer, pH 3.5, and ethyl acetate. After centrifugation the ethyl acetate was removed and a second partition with ethyl acetate was carried out. The pooled organic phases were evaporated and the residue was partitioned between n-heptane and methanol as described above. The separated methanol phase was evaporated and subjected to straight phase HPLC.

HPLC

Methanolic residues of scale extracts were applied to a Nucleosil 50-5μm silica column (25 cm x 4.9 mm i.d.) eluted with hexane/propan-2-ol/methanol/acetic acid (86:7:5:0.1, by vol.) at 1 ml/min. Effluent fractions (1 ml) were collected, evaporated, redissolved in 3 ml minimal essential medium buffered to pH 7.4 with 20 mM HEPES buffer (MEM) and subjected to the agarose microdroplet chemokinesis assay described below.

Methanolic residues of scale and chamber fluid extracts, to be analysed by GC-MS, were purified by an HPLC system comprising two 25 cm x 4.9 mm i.d. silica columns (Nucleosil 50-5μm and Spherisorb S5W columns in series) eluted with hexane/propan-2-ol/acetic acid (96:4:0.1, by vol.) at 1 ml/min. Effluent was monitored for ultraviolet absorbance at 235 nm. Appropriate fractions were collected, evaporated and derivatised by successive reaction with fresh methanolic ethereal diazomethane and BSTFA. The derivatised products were stored in excess BSTFA for GC-MS analysis.

Agarose microdroplet chemokinesis assay

Heparin (10 μg/ml) and dextran (1% v/v final concentration) were added to fresh venous blood obtained from normal volunteers. The mixture was left to stand for 1 hour at room temperature, after which the upper leukocyte rich layer was removed and centrifuged (350g for 15 min). Erythrocytes in the pellet were lysed by addition of 3 ml distilled water, the mixture being returned to isotonicity after 30 sec with 0.65M sodium chloride. Following centrifugation (350g for 5 min) the lysing process was repeated, the leukocytes (70-80% neutrophils) were washed in MEM and the concentration adjusted to 10^8 cells/ml. Chemokinesis was assayed using an agarose microdroplet technique (22). Samples were incubated for 2 hours at 37°C in a humidified atmosphere. The radial distance travelled by cells from the agarose droplet was determined for each sample by measurement of an image magnified 20 times by a projecting microscope. Chemokinetic movement was expressed as the radial distance moved by the leukocytes from the agarose droplet less spontaneous random movement seen when cells were incubated in the presence of buffer alone.

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Gas chromatography was carried out on a 25 m x 0.32 mm i.d. CP-Sil-19 CB quartz capillary column (Chrompak, London, England) appropriately heated in a Pye Unicam series 204 gas chromatograph. This was directly coupled to a VG 305 mass spectrometer controlled by a VG 2025 data system. All data were recorded under electron impact conditions at 40 eV and 4 kV accelerating potential. The source temperature was 200°C. Derivatised samples were applied to the capillary column with a dropping needle injector (Chrompak).

RESULTS

Fig. 2A illustrates chemokinetic activity in HPLC fractions of psoriatic scale extract. Fig. 2B shows a comparative elution profile of authentic 12-HETE, 5-HETE and LTB₄. Significant chemokinetic activity is seen in HPLC fractions with the same retention time as LTB₄ and the monoHETE compounds, especially 12-HETE. Similar results were obtained in three further experiments.

Fig. 3A shows a representative ultraviolet absorbance profile when a psoriatic scale extract is applied to the described two-column HPLC system. Fig. 3B shows the elution profile of a mixture of authentic hydroxy fatty acids. Both scale and chamber fluid extracts were purified by this system. Some of the peaks in Fig. 3A appear higher than would be expected from the measured levels of each hydroxy fatty acid (Table 2). Such peaks must contain material other than the corresponding hydroxy acid. Individual HPLC fractions corresponding to the retention times of each of the authentic hydroxy fatty acids shown in Fig. 3B were collected separately, with the exception of the poorly separated 11-HETE and 13-HODD fractions, which were pooled. The fractions were evaporated and derivatised for GC-MS as described.

Hydroxy fatty acid derivatives in purified chamber fluid and scale extracts were quantified by GC-MS with selected ion monitoring (GC-MS-SIM). Table 1 gives the ions monitored and the equivalent chain lengths of each measured derivative. Table 2 shows the concentrations of each hydroxy fatty acid. These values are uncorrected for recovery and are therefore semiquantitative. 5-HETE was undetectable in chamber fluid extracts, a finding possibly partly explained by experiments with deuterated 5-HETE, which indicated that the extraction, purification and GC-MS of this compound gave recoveries of less than 10% with these methods.

Conclusive identification of each of the hydroxy fatty acids indicated in Table 2, apart from 5-HETE, was achieved by obtaining the full mass spectrum of each compound in purified scale extracts. Spectra agreed with those of the authentic compounds synthesised by photooxidation of arachidonic and linoleic acids. Although 5-HETE was detectable in scale extracts by GC-MS-SIM, its apparently low levels did not allow a full mass spectrum to be obtained.
Fig. 2 A  Chemokinetic Activity in Straight Phase HPLC Fractions of an Extract of 150 mg Psoriatic Scale. A Nucleosil 50-5μm analytical column was eluted with hexane/propan-2-ol/methanol/acetic acid (88:7:5:0.1, by vol.) at 1 ml/min. Each point represents the mean of duplicate estimations.

B Comparative Elution Profile of Authentic 12-HETE (X), 5-HETE (Y) and LTB₄ (Z). HPLC column effluent was monitored for ultraviolet absorbance at 235 nm initially. The detector was adjusted to monitor at 280 nm at the time indicated.
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Fig. 3 A  Straight Phase HPLC of an Extract of 150 mg Psoriatic Scale. Two analytical silica columns, in series, were eluted with hexane/propan-2-ol/acetic acid (96:6:0.1, by vol.) at 1 ml/min. Effluent was initially monitored with a detector signal attenuation of 256 (Spectra-Physics SP84000 detector and SP4100 recorder/integrator). The attenuation was reduced to 8 at the time indicated.

B  Comparative Straight Phase HPLC of a Mixture of Authentic Monohydroxy Fatty Acids, Simultaneously Injected. A = 12-HETE, B = 15-HETE, C = 11-HETE, D = 13-HOED, E = 9-HETE, F = 9-HOED, G = 8-HETE and H = 5-HETE.
Table 1. Ions Monitored during Quantitative GC-MS-SIM Analysis of Purified Scale and Chamber Fluid Extracts

<table>
<thead>
<tr>
<th>MonohETE</th>
<th>m/z</th>
<th>Ion</th>
<th>Equivalent Chain Length of Derivative</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-HETE</td>
<td>335.2</td>
<td>M - C_{5}H_{11}^{+}</td>
<td></td>
</tr>
<tr>
<td>12-HETE</td>
<td>295.2</td>
<td>C_{13}H_{18}O_{3}TMS^{+}</td>
<td></td>
</tr>
<tr>
<td>11-HETE</td>
<td>225.2</td>
<td>C_{10}H_{16}O_{3}TMS^{+}</td>
<td>21.3</td>
</tr>
<tr>
<td>9-HETE</td>
<td>255.1</td>
<td>C_{10}H_{14}O_{3}TMS^{+}</td>
<td></td>
</tr>
<tr>
<td>8-HETE</td>
<td>265.2</td>
<td>C_{13}H_{20}O_{3}TMS^{+}</td>
<td></td>
</tr>
<tr>
<td>5-HETE</td>
<td>406.3</td>
<td>M^{+}</td>
<td></td>
</tr>
<tr>
<td>13-HODD</td>
<td>225.2</td>
<td>as 11-HETE</td>
<td>19.9</td>
</tr>
<tr>
<td>9-HODD</td>
<td>225.2</td>
<td>as 11-HETE</td>
<td></td>
</tr>
</tbody>
</table>

* the GC oven was heated to 225°C.

Table 2. Monohydroxy fatty acid levels in purified extracts of skin chamber fluid and psoriatic scale

<table>
<thead>
<tr>
<th>Monohydroxy acid</th>
<th>Scale (ng/2.5 mg)</th>
<th>Chamber fluid (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 3</td>
<td>Lesional Uninvolved</td>
</tr>
<tr>
<td></td>
<td>n = 4</td>
<td>n = 4</td>
</tr>
<tr>
<td>12-HETE</td>
<td>32 ± 19</td>
<td>104 ± 60</td>
</tr>
<tr>
<td>8-HETE</td>
<td>1.7 ± 0.6</td>
<td>0.5 ± 0.4</td>
</tr>
<tr>
<td>15-HETE</td>
<td>1.2 ± 0.5</td>
<td>1.4 ± 1.0</td>
</tr>
<tr>
<td>9-HETE</td>
<td>0.8 ± 1.0</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>11-HETE</td>
<td>0.4 ± 0.2</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td>5-HETE</td>
<td>0.1 ± 0.1</td>
<td>*</td>
</tr>
<tr>
<td>13-HODD</td>
<td>63 ± 45</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>9-HODD</td>
<td>6 ± 8</td>
<td>2.0 ± 0.3</td>
</tr>
</tbody>
</table>

* undetectable

Results are expressed either as ng hydroxy fatty acid per ml chamber fluid or as ng per 2.5 mg scale wet weight. The latter unit was chosen for convenience because abrasion of psoriatic lesions over an area of 3.5 cm² (the area covered by a skin chamber) yielded variable, low milligram amounts of scale. Mean values and standard deviations are shown. All results are uncorrected for recovery and are therefore semiquantitative. Results are expressed to the nearest ng, except where levels are less than 2 ng, when results are given to the nearest 0.1 ng.
During purification of each psoriatic scale extract, a fraction corresponding to the retention times of the poorly separated 11-HETE and 13-HODD was collected, as described. On GC-MS-SIM analysis of this derivatised fraction, the mass spectrometer was tuned to monitor m/z 225.2, which corresponds to the mass of an ion prominent in the spectra of both 13-HODD and 11-HETE. The trace shown in Fig. 4 was obtained and, as can be seen, at least 4 discrete components are present.

![Fig. 4 GC-MS-SIM Trace at m/z 225.2 of a Derivatised 13-HODD/11-HETE Fraction Obtained on HPLC of a Psoriatic Scale Extract.](image-url)
The first two peaks (I and II) correspond to the elution of 13-HODE and 11-HETE methyl ester trimethylsilyl ethers respectively. Peak III represented material present at too low a concentration for unambiguous identification, but peak IV was due to a substance present in sufficient quantity for a full mass spectrum (Fig. 5A). At m/z 410 is an apparent molecular ion, which is four units above the value for the molecular ion of a monoHETE methyl ester trimethylsilyl ether. This assignment is supported by the presence of ions at m/z 395 (M – CH3)+ and 320 (M – TMSOH)+, and this, together with the presence of two intense ions at m/z 339 and 225, strongly suggests that the molecule is a derivatised eicosadienoic acid with an hydroxyl group substituted at C15.

Fig. 5A Mass Spectrum of Material Forming Peak IV, Fig. 4.

In order to confirm this structure, 15-HEDE was prepared from the parent 11,14-eicosadienoic acid by photo-oxidation, as described. The natural and synthetic compounds, when derivatised to form their methyl ester trimethylsilyl ethers, gave identical equivalent chain lengths on gas chromatography (21.9). In addition, when synthetic 15-HEDE was applied to the 2-column HPLC system described above, it was found to have an identical retention time to that of 13-HODE. This is consistent with the detection of natural 15-HEDE in the collected 11-HETE/13-HODE HPLC fraction of psoriatic scale extracts. Finally, the synthetic material, after derivatisation, gave a mass spectrum (Fig. 5B) which agreed with that of the natural substance.

Studies of the biological activity of synthetic 9-HODE, 13-HODE and 15-HEDE (the latter two being mixed with the isomers described in the Methods section) were carried out, but these compounds were chemokinetically inactive in the agarose microdroplet assay in concentrations from 10-10 to 10-4M.

DISCUSSION

The data shown in Fig. 2 suggest that biologically active amounts of LTB4 and monoHETE-like material are present in the surface scale of psoriatic skin lesions. This result is compatible with the findings in skin chamber fluid from abraded psoriatic lesions (15). Further analysis by GC-MS of purified scale and chamber fluid extracts indicated that at least 9 monohydroxy fatty acids are present in psoriatic skin. These include the compounds listed in Table 2, and 15-HEDE. The latter was identified in scale extracts but not quantified in these samples, nor was its presence established in chamber fluid extracts. The biochemical source of 15-HEDE remains speculative, as its parent eicosadienoic acid has not previously been described in skin extracts.

The semiquantitative data in Table 2 suggest that, of the compounds measured, the hydroxy fatty acid present in highest concentration in chamber fluid was 12-HETE, followed by 13-HODE and 9-HODE. There were higher concentrations of each hydroxy fatty acid in chamber fluid from lesional as opposed to uninvolved skin with the exception of 9-HODE, although in some instances the differences were small. In addition, considerable amounts of monohydroxy fatty acids, particularly 13-HODE, 12-HETE and 9-HODE, were found in extracts of psoriatic scale.

These findings are consistent with those of Hammarström et al. (14), who reported elevated levels of 12-HETE in keratome slices of psoriatic lesional skin, as determined by GC-MS. Of the monoHETE compounds measured, 12-HETE was present in purified scale extracts in amounts sufficient to account, at least in part, for the monoHETE-like activity seen in Fig. 2A. The HODE compounds do not contribute to this activity, as neither has chemokinetic properties. The possibility that other chemokinetic compounds apart from 12-HETE are contributing to the monoHETE-like activity seen in Fig. 2A is currently under study, but 12-HETE
appears to be the only identified monohydroxy fatty acid of potential relevance to the psoriatic neutrophil infiltrate.

The fatty acid hydroperoxide intermediates 12-hydroperoxyeicosatetraenoic acid (12-HPETE), 15-HPETE and 13-hydroperoxyoctadecadienoic acid (13-HPODD) have been reported to activate soluble splenic cell guanylate cyclase (23), and 12-HETE has been shown to activate soluble guanylate cyclase in psoriatic epidermal cells (24). By thus elevating epidermal cyclic 3',5'-guanosine monophosphate, these compounds may mediate the enhanced rates of epidermal proliferation characteristic of psoriasis.

The hydroperoxy precursors of the HETE and HPOD compounds may also be relevant to the cellular and vascular events of the inflammatory process in psoriasis. While 5-, 11- and 15-HPETE are chemokinetic for human neutrophils and are as potent or more potent than their corresponding hydroxy acids (12,25), the leukocyte stimulating properties of the HPOOD compounds have yet to be reported. The 5-, 11- and 12-HPETE intermediates are also vasodilators in isolated perfused vascular preparations (26), both 15-HPETE and 13-HPODD augment anaphylactic mediator release (27), and 13-HPODD induces airways hyperactivity (28) and stimulates arterial smooth muscle (29).

Interest has arisen in the modulating effects of 15-HETE on lipoxygenase enzyme systems. It has been shown to be an inhibitor of platelet 12-lipoxygenase (30) and of polymorphonuclear leukocyte (31) and T-lymphocyte (32) 5-lipoxygenase, as well as of lipoxygenases in certain cell lines (33). In contrast, it has been reported to activate a 5-lipoxygenase in a murine mast cell/basophil line by a mechanism thought to be highly cell- and enzyme-specific. Substitution of the n-6 position of 15-HEIE appears important for these properties (30,32,33). If this is the case, both 13-HODD and 15-HEDE, which possess the hydroxy group at n-6, may have similar properties. It is therefore possible that 15-HETE, 15-HEDE and 13-HOCC, particularly the latter, which is present in psoriatic lesional skin in very large amounts, may have modulating effects on the lipoxygenase pathways in psoriasis. In support of this possibility is the finding that 15-HEDE, as well as 15-HETE, inhibited lipoxygenase activity in mouse spleen lymphocyte cultures (34).

To date, the lesional and uninvolved skin of psoriatic patients remain the only human tissues in which the endogenous production of monohydroxy metabolites of arachidonic, linoleic or 11,14-eicosadienoic acids has been conclusively reported, although it is likely that other tissues will produce these compounds in vivo. Little is known about the cellular source of these compounds in skin, although it has been reported that suspensions of mouse epidermal cells are capable of synthesising 12-HETE (35). Further studies are being directed towards the development of quantitative GC-MS-SIM assays for these compounds. Such assays should help to clarify the pathogenetic significance of these hydroxy fatty acids in psoriasis, but more positive clarification will depend on the availability of specific antagonists or lipoxygenase inhibitors.
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