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Biosynthesis, biological effects, and receptors of hydroxyeicosatetraenoic acids (HETEs) and oxoeicosatetraenoic acids (oxo-ETEs) derived from arachidonic acid

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Abstract

Arachidonic acid can be oxygenated by a variety of different enzymes, including lipoxygenases, cyclooxygenases, and cytochrome P450s, and can be converted to a complex mixture of oxygenated products as a result of lipid peroxidation. The initial products in these reactions are hydroperoxyeicosatetraenoic acids (HpETEs) and hydroxyeicosatetraenoic acids (HETEs). Oxoeicosatetraenoic acids (oxo-ETEs) can be formed by the actions of various dehydrogenases on HETEs or by dehydration of HpETEs. Although a large number of different HETEs and oxo-ETEs have been identified, this review will focus principally on 5-oxo-EETE, 5S-HETE, 12S-HETE, and 15S-HETE. Other related arachidonic acid metabolites will also be discussed in less detail. 5-Oxo-EETE is synthesized by oxidation of the 5-lipoxygenase product 5S-HETE by the selective enzyme, 5-hydroxyeicosanoid dehydrogenase. Its actions are mediated by the selective OXE receptor, which is highly expressed on eosinophils, suggesting that it may be important in eosinophilic diseases such as asthma. 5-Oxo-EETE also appears to stimulate tumor cell proliferation and may also be involved in cancer. Highly selective and potent OXE receptor antagonists have recently become available and could help to clarify its pathophysiological role. The 12-lipoxygenase product 12S-HETE acts by the GPR31 receptor and promotes tumor cell proliferation and metastasis and could therefore be a promising target in cancer therapy. It may also be involved as a proinflammatory mediator in diabetes. In contrast, 15S-HETE may have a protective effect in cancer. In addition to GPCRs, higher concentration of HETEs and oxo-ETEs can activate peroxisome proliferator-activated receptors (PPARs) and could potentially regulate a variety of processes by this mechanism.

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Keywords

Inflammation; Cancer; Asthma; 5-Oxo-EETE; OXE receptor; 12-HETE

1. Introduction

Arachidonic acid (AA) is a key polyunsaturated fatty acid (PUFA), which serves as the precursor for a wide variety of lipid mediators that are involved in many physiological and pathophysiological processes. The initial step in the formation of these mediators is introduction of oxygen, which can be catalyzed by lipoxygenases, cyclooxygenases, or cytochrome P450 enzymes. In the cases of lipoxygenases and cyclooxygenases, AA is first converted to hydroperoxy products (HpETEs, hydroperoxyeicosatetraenoic acids), which can serve as precursors for different intermediates such as prostaglandin (PG) H_2 or leukotriene (LT) A_4 or biological mediators such as hepoxilins [172], lipoxins (LXs) [9], and eoxins [36] (Fig. 1). PGH_2 is converted by specific synthases to PGs D_2 , E_2 , $F_{2\alpha}$, and I_2 and thromboxane (TX) A_2 [221], all of which have a variety of biological effects mediated by the DP_{1-2} , EP_{1-4} , FP, IP, and TP prostanoid receptors [97]. LTA_4 is enzymatically converted to either the potent neutrophil chemoattractant LTB_4 or to LTC_4 , the precursor of LTD_4 , a potent proinflammatory mediator in asthma [80]. The actions of LTB_4 are mediated by the BLT_1 receptor, whereas those of LTD_4 are mediated by the $cysLT_1$ and $cysLT_2$ receptors. LTA_4 can also serve as a precursor for the 12-LO or 15-LO-catalyzed formation of LXA_4 , which interacts with the ALX receptor, and LXB_4 [215].

Alternatively, HpETEs generated by lipoxygenases and cyclooxygenases can be reduced by peroxidases to monohydroxy fatty acids (HETEs, hydroxyeicosatetraenoic acids), which are the subject of the present review. Since the initial oxygenase-catalyzed abstraction of a hydrogen atom is from a methylene group situated between two double bonds, the hydroperoxyl group in HETEs formed in this way is always adjacent to a conjugated diene system (Fig. 2). The hydroperoxyl/hydroxyl groups of HpETEs and HETEs formed by lipoxygenases are usually, but not always, in the S-configuration.

In contrast to lipoxygenases, cytochrome P450 enzymes can introduce a hydroxyl group in a variety of positions, resulting in products that in most cases lack a conjugated diene chromophore (e.g. 20-HETE). Rather than hydroperoxy-fatty acids, the initial products of these reactions are hydroxy-fatty acids formed by the introduction of a single oxygen atom from O_2 bound to Fe^{3+} at the active site of the enzyme [104]. A mixture of R and S HETE enantiomers is usually formed by cytochrome P450 enzymes, with the R enantiomer tending to predominate, especially in the case of 12-HETE [29,169].

Oxoeicosatetraenoic acids (oxo-ETEs), also sometimes referred to as KETEs (keto-ETEs), can be formed by the oxidation of HETEs by different positionally-selective dehydrogenases (Fig. 1). Alternatively, they can be formed either enzymatically or non-enzymatically directly from HpETEs. Although not studied in as much detail as LTs and PGs, HETEs and oxo-ETEs have a variety of biological effects and may be implicated in a number of diseases including asthma, cancer, and diabetes. Because of the large number of publications in this area, this review is of necessity rather selective and will be restricted to metabolites of

arachidonic acid, even though monohydroxy fatty acids derived from other PUFA are certainly of interest. 5-Oxo-ETE and 12S-HETE have a number of interesting properties and these, in particular those related to 5-oxo-ETE, will be the major focus. Other HETEs and oxo-ETEs will be discussed in less detail.

2. Formation of HETEs

2.1. Lipoxygenase pathways

The predominant pathway for the formation of HETEs is the peroxidase-catalyzed reduction of HpETEs generated by various lipoxygenases. These enzymes are widely distributed in animals, plants, and fungi [18], as well as in some bacteria [88]. Although mammalian lipoxygenases (LOs) are named according to the position of AA at which they introduce a molecule of oxygen, AA is not necessarily the preferred substrate. The major sites of oxidation of AA are in the 5-, 12-, and 15- positions, and these reactions are catalyzed by 5-LO, 12-LO, and 15-LO enzymes. The reaction products are usually almost exclusively in the S configuration, although there are some exceptions as mentioned below.

A major pathway for the metabolism of AA is initiated by the action of 5-LO in the presence of the nuclear membrane-associated accessory protein FLAP (5-LO activating protein). 5-LO, encoded by the *ALOX5* gene, is highly expressed in most types of inflammatory cells with the exception of T lymphocytes [60,198]. It initially oxidizes AA to 5S-HpETE, which either dissociates from the enzyme and is reduced to 5S-HETE by peroxidase, or remains bound and is converted to LTA₄, the substrate for LTC₄ synthase and LTA₄ hydrolase, resulting in the formation of LTC₄ and LTB₄, respectively.

Another pathway for the oxygenation of AA is catalyzed by “platelet-type” 12S-LO [85], which is encoded by the *ALOX12* gene and is found principally in platelets, keratinocytes, and certain tumor cells [80]. It is highly regio- and stereo- specific, producing 12S-HpETE, which can be subsequently reduced to 12S-HETE. Although 12S-HETE is almost always found as the S-enantiomer, there is another lipoxygenase in human skin (12R-LO) that converts AA to 12R-HpETE [16]. This enzyme may be the source of the 12R-HETE that is found in psoriasis [7,251] and may play a role in this disease [64]. However, the primary function of 12R-LO may be the oxidation of O-linoleoyl ω -hydroxyceramide, a required step in the formation of the ω -hydroxyceramides that are required for the formation of the mammalian skin barrier [263].

15-LO-1 (12/15-LO) is encoded by the *ALOX15* gene and converts AA to a mixture of 12S-HpETE and 15S-HpETE, the ratio varying from one species to another. In humans 15-LO-1 is highly expressed in eosinophils and epithelial cells, the principal product being 15S-HpETE, the precursor of 15S-HETE [80]. 15-LO-1 is also involved in the production of lipoxins [34] and eoxins [62]. In contrast, 15-LO-1 in mice converts AA principally to 12S-HETE and is found mainly in macrophages [80]. A second 15-lipoxygenase (15-LO-2, encoded by *ALOX15B*) has been identified in humans [20]. This enzyme converts AA exclusively to 15S-HpETE and is found in hair roots, prostate, lung, and cornea. It has also been identified in macrophages within human atherosclerotic plaques [67,106] and is

induced by hypoxia inducible factor-1 α [106]. The murine ortholog of this enzyme converts AA to 8S-HETE [111].

2.2. Cyclooxygenase

Although the primary products of cyclooxygenase (COX)-1 and COX-2 are prostaglandins, these enzymes also convert AA to small amounts of 11- and 15- HpETE, which are subsequently converted by the peroxidase activity of these enzymes to the corresponding HETEs [91,185]. 11-HETE generated by both COX-1 and COX-2 is exclusively in the R-configuration [236,252]. 15-HETE derived from COX-2 is also in the R configuration [252], whereas COX-1 gives rise to both 15S-HETE and 15R-HETE [236]. Although aspirin efficiently blocks prostaglandin formation by COX-2, it does not prevent the formation of 15R-HETE, which becomes the major AA metabolite produced under these conditions [99,128]. Aspirin-acetylated COX-2 is also responsible for the formation of the “aspirin-triggered lipoxin” 15-epi-LXA₄ [37].

2.3. Cytochrome P450

Lipoxygenases and cyclooxygenases initiate the addition of molecular oxygen by abstracting a hydrogen atom specifically from a methylene group at the center of a 1Z,4Z-pentadiene system, resulting in the introduction of a hydroperoxy group adjacent to a conjugated diene system. In contrast, cytochrome P450 enzymes can hydroxylate AA at many different positions [201]. In general, three types of product are formed: (i) ω -hydroxy metabolites, (ii) bisallylic hydroxylation products, in which the hydroxyl group is added to a methylene group situated between two cis double bonds, and (iii) HETEs similar to those formed by lipoxygenases, in which the hydroxyl group is adjacent to a conjugated diene system. A variety of ω -hydroxy metabolites of AA have been identified, including 16-HETE, 17-HETE, 18-HETE, 19-HETE, and 20-HETE [30,58,238]. Of these, 20-HETE has received by far the most attention because of its potent vasoconstrictor effects on small arteries and arterioles and on ion transport in the kidney [201]. Liver microsomes and various cytochrome P450 enzymes also hydroxylate the three bisallylic carbons of AA to give 7-HETE, 10-HETE, and 13-HETE. The latter compounds are unstable in acidic conditions and can rearrange to give conjugated diene HETEs. 13-HETE can give rise to 11- and 15- HETE whereas 10-HETE can be converted to 8- and 12- HETE [19]. However, conjugated diene HETEs are also formed directly by cytochrome P450 isoforms [28], including 15R-HETE [169] and 12R-HETE [19,26,209], as well as 9-HETE and 11-HETE [28].

2.4. Lipid peroxidation

The six conjugated diene HpETEs and their HETE reduction products (i.e. 5-, 8-, 9-, 11-, 12-, and 15- HETE) are formed as early AA-derived products during lipid peroxidation [182]. Although HETEs formed as a result of lipid peroxidation could be derived from free AA, they most commonly occur esterified to lipids, as this is the most abundant storage site for AA in cells. Unlike enzymatically-derived AA metabolites, eicosanoids formed by lipid peroxidation have a variety of stereochemical configurations and HpETEs and HETEs formed by this process are racemic mixtures of R- and S- enantiomers. Esterified HETEs and oxo-ETEs are further discussed in section 3.4.

3. Formation of oxo-ETEs

HETEs are converted to oxo-ETEs by a number of regioselective dehydrogenases in the presence of NAD^+ or NADP^+ (Fig. 2). In some cases oxo-ETEs can also be formed directly from HpETEs either enzymatically or non-enzymatically.

3.1. HETE dehydrogenases

3.1.1. Biosynthesis of 5-oxo-EETE by 5-hydroxyeicosanoid dehydrogenase (5-HEDH)—5-Oxo-EETE is formed by the oxidation of the 5-LO product 5-HETE by 5-HEDH (Fig. 3), which was first discovered in human neutrophils [192] and subsequently shown to be present in a variety of other cell types, including many types of inflammatory cells, platelets, structural cells, and tumor cells [196]. The sequence of 5-HEDH has not yet been determined. Among inflammatory cells, neutrophils [192], monocytes [262], and B lymphocytes [74] display particularly high 5-HEDH activity. This enzyme is also highly expressed in epithelial [55] and endothelial [56] cells as well as various tumor cell lines [55,75]. Although the latter cells display little or no 5-LO activity, they could participate in the transcellular biosynthesis of 5-oxo-EETE by oxidizing inflammatory cell-derived 5-HETE as we have shown to be the case with PC3 prostate tumor cells coincubated with neutrophils [75].

5-HEDH is a microsomal enzyme that is highly selective for 5S-HETE. Little or no metabolism is observed for 5R-HETE [193] or positional isomers in which the hydroxyl group is present in other positions (8, 9, 11, 12, or 15) [192]. In addition, it requires a 6-trans double bond adjacent to the 5S-hydroxyl group [192] and a fatty acid chain length of at least 16 carbons [173]. DiHETEs that contain a 5S-hydroxy group followed by a 6-trans double bond are also oxidized by 5-HEDH, although at a lower rate than 5S-HETE [192]. This includes 6-trans isomers of LTB_4 , 5S,12S-diHETE, and 5S,15S-diHETE, but not LTB_4 , as it contains a 6-cis double bond. Addition of a hydroxyl group to the ω -end of 5S-HETE dramatically reduces oxidation by 5-HEDH, suggesting that the terminal portion of the molecule must be hydrophobic to permit efficient metabolism [195].

5-HEDH has an absolute cofactor requirement for NADP^+ and displays a 10,000-fold preference for this pyridine nucleotide over NAD^+ [54]. The K_m of 5-HEDH for NADP^+ (140 nM) is even lower than that for 5S-HETE (670 nM). In contrast, enzyme activity is strongly inhibited by NADPH [54], and hence it is the ratio of NADP^+ to NADPH, rather than the absolute concentration of NADP^+ , that is critical for regulating 5-oxo-EETE formation. Because cells maintain a very high intracellular ratio of NADPH to NADP^+ , they have only a very limited ability to synthesize 5-oxo-EETE under baseline unstimulated conditions, even if they express high levels of 5-HEDH. For example, resting unstimulated neutrophils convert 5S-HETE principally to its ω -oxidation product 5,20-diHETE, probably by the action of NADPH-dependent LTB_4 20-hydroxylase (CYP4F3) [167,197]. However, activation of the respiratory burst in these cells, in which superoxide generation is coupled to oxidation of NADPH to NADP^+ , results in a dramatic increase in 5-oxo-EETE formation and a reduction in 5,20-diHETE [193]. Activation of NADPH oxidase in other types of phagocytic cells, including monocytes [262] and eosinophils [187], has similar effects on 5-oxo-EETE synthesis. Oxidative stress is another potent activator of 5-oxo-

ETE formation in nearly all cell types containing 5-HEDH, with the notable exception of neutrophils [55–57,75]. Cell death in neutrophils [73] and tumor cells [75] also strongly promotes the oxidation of 5-HETE to 5-oxo-ETE, probably as a result of associated oxidative stress. Both oxidative stress and cell death are associated with dramatic increases in intracellular GSSG, which is reduced back to GSH by the NADPH-dependent enzyme glutathione reductase, thereby generating the high levels of NADP⁺ required by 5-HEDH.

Conditions favoring the synthesis of 5-oxo-ETE (activation of the respiratory burst in inflammatory cells, oxidative stress, and dying cells) are prevalent during inflammation and should provide highly favorable conditions for the NADP⁺-dependent synthesis of 5-oxo-ETE (Fig. 4). This mediator could be produced during chronic inflammatory disorders and could contribute to prolonged inflammation due to its proinflammatory effects as discussed in Section 4.1.

3.1.2. Formation of 12-oxo-ETE by 12-HEDH and its further metabolism to dihydro products—

We identified a microsomal enzyme in porcine neutrophils that oxidizes 12-HETE to 12-oxo-ETE in the presence of NAD⁺ [244] (Fig. 5). We refer to this enzyme as 12-hydroxyeicosanoid dehydrogenase (12-HEDH), as it also oxidizes other 12-hydroxyeicosanoids, including LTB₄. Interestingly, 12-HEDH does not appear to distinguish between 12R-HETE and 12S-HETE, as both are metabolized equally well, although the possibility that distinct 12R-selective and 12S-selective enzymes exist cannot be ruled out. 12-Oxo-ETE is further metabolized in porcine neutrophils by the NADH-dependent cytosolic enzyme, 12-oxoeicosanoid ¹⁰-reductase, to 12-oxo-6,8,14-eicosatrienoic acid (12-oxo-ETrE; i.e. 10,11-dihydro-12-oxo-ETE). 12-Oxo-ETrE is reduced to 12R-hydroxy-5,8,14-eicosatrienoic acid (12R-HETrE; i.e. 10,11-dihydro-12S-HETE) along with smaller amounts of 12S-HETrE [243,244]. Note that 12S-HETE and 12R-HETrE have identical stereochemical configurations at C₁₂, but are designated as “S” and “R” respectively because of the priority rules. The latter reaction could possibly be catalyzed by 12-HEDH acting in the reverse direction or by a 12-ketoreductase similar to the microsomal NADH-dependent enzyme identified in rat skin and neutrophils [61]. The above pathway resembles a similar one in rabbit [157] and bovine [253] corneal epithelial cells in which the cytochrome P450 product 12R-HETE is converted to the above 12-oxo-10,11-dihydro and 10,11-dihydro metabolites, presumably with 12-oxo-ETE as an intermediate. As with porcine neutrophils, both 12R-HETE and 12S-HETE are substrates for this pathway. A similar pathway leading to the formation of 12-oxo-ETE and its 10,11-dihydro derivatives exists in keratinocytes [50].

12-HEDH is distinct from another enzyme (LTB₄ 12-hydroxy dehydrogenase) that converts LTB₄ to 12-oxo-LTB₄ [256]. Unlike 12-HEDH, the latter enzyme is found in the cytosol and requires NADP⁺ as a cofactor. Although it oxidizes other 5,12-diHETEs, 12-HETE is not a substrate. LTB₄ 12-hydroxy dehydrogenase is highly expressed in liver, kidney, and intestine, but not in leukocytes [257]. In addition to its dehydrogenase activity, this enzyme also acts as a ¹³-reductase, converting 15-oxoprostaglandins [52] and 15-oxo-LXA₄ [39] to 13,14-dihydro metabolites. As 15-oxoprostaglandins are its preferred substrates it is also known as 15-oxoprostaglandin 13-reductase.

3.1.3. Oxidation of 15-HETE and other eicosanoids by 15-

hydroxyprostaglandin dehydrogenase (15-PGDH)—15-PGDH is a critical enzyme for the metabolism and biological inactivation of PGs [231]. It is found in the cytosol of many different cell types and requires NAD⁺ as a cofactor. In addition to prostaglandins, 15-PGDH oxidizes a variety of other ω 6-hydroxyeicosanoids, including 15S-HETE [1,11], 12-hydroxy-5,8,10-hydroxyheptadecatrienoic acid (12-HHT) [135], and LXA₄ [214] as well as ω 6-hydroxy derivatives of other fatty acids, such as 13-hydroxyoctadecadienoic acid [1]. Interestingly, 11R-HETE, generated by COX-2 in epithelial cells, is also a substrate for 15-PGDH, being converted to 11-oxo-EETE [134]. 11-Oxo-EETE was found to inhibit the proliferation of both endothelial cells and LoVo colon cancer cells [222].

3.2. Formation of oxo-EETs by other enzymatic pathways

Although oxo-EETs are likely to be more commonly formed by the enzymatic oxidation of HETEs, they can also be formed directly from HpEETs by the actions of cytochrome P450 isozymes [24]. Human CYP2S1, and to a lesser extent several other cytochrome P450 isoforms, were found to convert 5S-HpETE, 12S-HpETE, and 15S-HpETE to 5-oxo-EETE, 12-oxo-EETE, and 15-oxo-EETE, respectively [24]. 15-Oxo-EETE has also been identified following incubation of 15S-HpETE with rat liver microsomes containing cytochrome P450 enzymes [32].

Another pathway for the direct formation of oxo-EETs from HpEETs involves mammalian epidermal lipoxygenase type 3 (*eLOX3*) [259]. This enzyme converts 12R-HpETE to 12-oxo-EETE along with the heptoxilin A₃ isomer 8R-hydroxy-11R,12R-epoxyeicosa-5Z,9E,14Z-trienoic acid. 8R-HpETE, 12S-HpETE, and 15S-HpETE are also substrates, but are converted less efficiently than 12R-HpETE.

A cytosolic NAD⁺-dependent dehydrogenase that converts 13S-hydroxy-9,11-octadecadienoic acid (13S-HODE) to 13-oxo-9,11-octadecadienoic acid has been identified in intestine and liver, with lower expression in several other tissues [25]. Because little activity was detected in the lungs, this enzyme was thought to be distinct from 15-PGDH. Although 13-HODE is the preferred substrate, it also converts 15S-HETE to 15-oxo-EETE and, to a lesser extent, 12S-HETE to 12-oxo-EETE [22].

3.3. Nonenzymatic formation of oxo-EETs

It is well known that hydroperoxy PUFA undergo dehydration to the corresponding oxo fatty acids, especially in the presence of heme compounds [82]. Therefore, in circumstances in which HpEETs tend to accumulate, oxo-EETs can be formed nonenzymatically. This mechanism probably accounts for the formation of 5-oxo-EETE by murine macrophages, which do not express 5-HEDH [261]. 5-HpETE was converted to 5-oxo-EETE in the presence of a heat-stable cytosolic factor from these cells, consistent with nonenzymatic dehydration as referred to above. 5-Oxo-EETE was also previously detected after incubation of AA with a cytosolic fraction from murine MC-9 mast cells and was likely formed by dehydration of 5-HpETE by a similar mechanism [23].

Other oxo-ETEs can be formed similarly from HpETEs. For example, 12-oxo-ETE was detected following incubation of human platelets with AA [66]. This compound was also formed after incubation of 12-HpETE with boiled platelets, indicating that this was a nonenzymatic reaction. This was supported by the finding that incubation of 12-HpETE with heme compounds in the absence of platelets also led to the formation of 12-oxo-ETE. 12-Oxo-ETE was also identified after incubation of either AA or 12-HpETE with homogenates of *Aplysia* neural tissue [181].

3.4. Esterified HETEs and oxo-ETEs

HETEs, similarly to PUFA, are rapidly incorporated into cellular lipids. 5S-HETE produced following activation of neutrophils, is incorporated into both triglycerides and phospholipids, principally phosphatidylcholine (PC) and phosphatidylethanolamine (PE) [226]. The precise neutrophil phospholipid species containing 5-HETE have recently been identified in a lipidomic analysis as the plasmalogens 18:0p/5-HETE-PE, 18:1p/5-HETE-PE, and 16:0p/5-HETE-PE, and to acyl-linked 16:0a/5-HETE-PC [38]. 5-Oxo-ETE is also rapidly incorporated into neutrophil lipids, being found mainly in the triglyceride fraction [166]. Similarly, 5-HETE, 12-HETE, and 15-HETE are incorporated into macrophage lipids [176,225], with the highest levels being found in neutral lipids, phosphatidylcholine, and phosphatidylinositol. Activation of platelets leads to the rapid activation of 12-LO and the incorporation of 12-HETE into phosphatidylethanolamine and phosphatidylcholine to give the following plasmalogen and acyl lipids: 16:0p/12S-HETE-PE, 18:1p/12S-HETE-PE, 18:0p/12S-HETE-PE, 18:0a/12S-HETE-PE, 16:0a/12S-HETE-PC, and 18:0a/12S-HETE-PC [235]. Incorporation of HETEs into lipids appears to be a fairly general phenomenon and has also been observed in a number of other cell types, including both epithelial [2] and endothelial [245] cells.

The esterified HETEs discussed above are formed following their biosynthesis from free AA. However, esterified HETEs and oxo-ETEs can also arise due to the direct oxidation of esterified AA, which can occur both enzymatically and nonenzymatically. Although most of the enzymes that oxygenate AA exhibit little or no activity on AA that is esterified to phospholipids, 15-LO-1 is an exception, and readily oxidizes esterified AA, producing esterified 12-HpETE and 15-HpETE along with their reduction products 12-HETE and 15-HETE [232]. In this way 15-LO-1 may initiate lipid peroxidation, which could be either beneficial (e.g. maturation of reticulocytes) or detrimental (e.g. oxidation of LDL) [206]. 15-Oxo-ETE esterified to PE was identified in human monocytes following induction of 15-LO-1 in these cells with IL-4 [86]. Interestingly, 15-PGDH was responsible for its formation from 15-HETE-PE. In contrast, murine peritoneal macrophages synthesized 12-oxo-ETE-PE, which was dependent on the presence of 15-LO-1 in these cells. Esterified oxo-ETEs have also been detected in human sebocytes [49]. Monoacylglycerols can also be substrates for lipoxygenases, as both 15-LO-1 and 15-LO-2 readily convert 2-arachidonylglycerol to 15-hydroxyeicosatetraenoic acid glyceryl ester [121].

Esterified PUFA are the primary targets in non-enzymatic lipid peroxidation and esterified HpETEs, HETEs, and oxo-ETEs are early products formed in this process. Esterified 5-, 8-, 9-, 11-, 12-, and 15- HETE were all detected in LDL following exposure to either

endothelial cells or Cu^{++} [247]. Similar results were obtained following exposure of human red blood cells to t-butyl hydroperoxide [151]. In this case, 5-HETE was the most abundant HETE detected in all of the phospholipid classes analyzed. Significant amounts of 5-oxo-EETE were also present in red cell membranes and were presumably formed by loss of H_2O from 5-HpETE [81]. Examination of HPLC column fractions for their ability to mobilize intracellular calcium in human neutrophils revealed that 5-oxo-EETE was by far the most potent among the compounds detected [81]. In model systems employing $\text{Cu}^{++}/\text{H}_2\text{O}_2$, $\text{Fe}^{++}/\text{H}_2\text{O}_2$, or 2,2'-azobis(2-amidinopropane)hydrochloride to oxidize 16:0p/AA-PC, 5-oxo-EETE along with all of the above HETEs, with the exception of 15-HETE, were detected [118].

HETEs and oxo-EETs esterified to phospholipids could serve as a source of free HETEs and oxo-EETs, released as a result of PLA_2 -catalyzed hydrolysis [21,114]. Relatively little information is available on the selectivity of phospholipases for the hydrolysis of phospholipids containing H(p)ETEs compared to AA. Although cPLA_2 is selective for the hydrolysis of phospholipids containing AA in the *sn*-2 position compared to other fatty acids, it can also hydrolyze phospholipids containing HETEs or HpETEs in this position. Phosphatidylcholine species containing either AA, 15-HETE, or 15-HpETE in the *sn*-2 position were hydrolyzed by cPLA_2 at comparable rates [31]. However, when present in mixtures, AA-containing phosphatidylcholine was hydrolyzed a faster rate than H(p)ETE-containing phosphatidylcholine. Similar results were obtained with secretory PLA_2 enzymes from pancreas and snake venom.

Alternatively, esterified H(p)ETEs could have biological effects in their own right, such as stimulation of cytokine release, activation of protein kinases, and activation of peroxisome proliferator-activated receptors (PPARs) [87]. 15S-HETE-substituted diacyl glycerol was reported to directly activate $\text{PKC-}\alpha$ and to inhibit diacylglycerol-induced activation of $\text{PKC-}\alpha$, $\text{PKC-}\delta$, $\text{PKC-}\beta_1$, and $\text{PKC-}\beta_{II}$ [3].

4. Biological actions of HETEs and oxoEETs

The determination of the biological roles of HETEs and oxo-EETs has been somewhat hampered in the past by the paucity of highly selective inhibitors of 12S-LO and 15-LO, although there are now several potent and selective 12S-LO inhibitors available [137]. Furthermore, the formation of these products by lipoxygenases is accompanied by the generation of a variety of other biologically active products. Therefore, it may be difficult to attribute the effects of selective LO inhibitors or gene deletions to any one substance. Although there are a number of excellent 5-LO inhibitors and FLAP antagonists, this pathway generates many biologically active products, including leukotrienes, lipoxins, resolvins, and protectins [80,215], in addition to 5-oxo-EETE. Similarly, 12-LO initiates the formation of hepoxilins as well as 12-HETE and can also be involved in the synthesis of lipoxins. 15-LO can also initiate the formation of lipoxins as well as eoxins and other products in addition to 15-HETE. Another issue is that dedicated receptors have not yet been identified for most members of this group of compounds and, with the exception of 5-oxo-EETE, there are no selective antagonists. The only well-established receptor for HETEs and oxo-EETs is the OXE receptor for 5-oxo-EETE [102,113,233]. In addition, a receptor for

12S-HETE (GPR31) has also recently been identified [78]. Nevertheless, HETEs and oxo-ETEs are produced by many types of cells and have been found to have a variety of effects and may be involved in a number of diseases.

4.1. Biological effects of 5-oxo-ETE

4.1.1. Effects of 5-oxo-ETE on neutrophils—The high degree of selectivity of 5-HEDH for 5S-HETE [192] suggested that the product of this reaction, 5-oxo-ETE, should have some biological function. Prior to the discovery of this pathway, 5S-HETE was known to activate neutrophils [161]. Although this effect appeared to be mediated by a receptor distinct from those of other lipid mediators such as LTB₄ and platelet-activating factor (PAF), its relatively low potency was not really consistent with a physiological role for this substance. We found that 5-oxo-ETE is a powerful activator of calcium mobilization and migration of human neutrophils with a potency about 100 times greater than that of 5S-HETE [191]. Furthermore, 5-oxo-ETE and 5S-HETE desensitized neutrophils to one another but not to LTB₄, indicating that they act by the same receptor. Subsequently, 5-oxo-ETE was found to induce a variety of other responses in neutrophils, including actin polymerization [158,189], increased surface expression of CD11b and CD11c [189], aggregation [160], and adherence [189]. Although 5-oxo-ETE on its own has relatively weak effects on neutrophil degranulation, when added to neutrophils pretreated with either TNF- α [159] or G-CSF [162], or in the presence of low concentrations of PAF or ATP [160], it is a potent activator of this response. Similarly, 5-oxo-ETE by itself induces little [158] or no [162] superoxide production in unprimed neutrophils, but elicits a robust response in GM-CSF-primed cells [162] or in the presence of low concentrations of PAF [160]. When administered intradermally to humans 5-oxo-ETE induces infiltration of neutrophils into the skin, but to a lesser extent than eosinophils [147] (see Section 4.1.5 below).

Although 5-oxo-ETE clearly activates neutrophils by its own selective receptor (see Section 4.1.3) it is only about one-tenth as potent as LTB₄. Since in many situations LTB₄ and 5-oxo-ETE would be produced concomitantly following activation of 5-LO in inflammatory cells, the physiological significance of 5-oxo-ETE as a neutrophil agonist is somewhat uncertain. However, it may play a role in certain circumstances where responses to LTB₄ have been blunted due to desensitization of the BLT₁ receptor because of exposure to endogenous LTB₄ [139]. There could also be temporal differences in LTB₄ and 5-oxo-ETE levels following inflammatory stimuli, with LTB₄ being more prominent acutely but 5-oxo-ETE persisting over a longer period of time [73]. It is therefore possible that in chronic or prolonged inflammation 5-oxo-ETE could contribute to neutrophil infiltration.

A recent study suggests that 5-oxo-ETE could play an important protective role in promoting tissue damage-induced leukocyte (neutrophils and/or macrophages) infiltration in a zebrafish model [53]. Epithelial damage results in exposure of the underlying cells to the external hypotonic medium, which promotes cell swelling accompanied by activation of cPLA₂ and 5-LO and the synthesis of (presumably) 5-oxo-ETE, which induces leukocyte migration to the site of injury. This could be prevented by knockdown of cPLA₂ or the 5-oxo-ETE receptor as well as by 5-LO inhibitors, but not by manipulations blocking the

actions of PGs or LTB₄. Moreover, 5-oxo-ETE induced in vivo leukocyte tissue infiltration in zebrafish, consistent with a role for this substance in host defence in this species.

4.1.2. Effects of metabolic alteration of 5-oxo-ETE on biological activity—The biological effects of 5-oxo-ETE can be altered or terminated by the actions of a number of enzymes (Fig. 3). 5-Oxo-ETE can be converted to three 5-oxo-HETEs with very different consequences. 5-Oxo-12-HETE, formed by platelet 12-LO during platelet/neutrophil coincubations, does not itself affect intracellular calcium levels in neutrophils, but blocks 5-oxo-ETE-induced calcium mobilization [190]. The 15-LO product 5-oxo-15-HETE is an agonist and, although not as potent as 5-oxo-ETE, promotes eosinophil migration [165,187,210] (see Section 4.1.5). In contrast, the cytochrome P450 product 5-oxo-20-HETE has little activity, retaining only 1% the potency of 5-oxo-ETE in mobilizing calcium in neutrophils. Although it is likely that the 20-hydroxylation of 5-oxo-ETE [195] (and 5S-HETE [167]) in neutrophils is catalyzed by LTB₄ 20-hydroxylase, which is highly expressed in these cells, this remains to be proven. LTC₄ synthase catalyzes the 1,4-Michael addition of GSH to 5-oxo-ETE to give 5-oxo-7-glutathionyl-8,11,14-eicosatrienoic acid (FOG₇), which promotes eosinophil migration, presumably by a mechanism distinct from that of 5-oxo-ETE because of the substantial structural differences [17,96]. Finally, reduction of 5-oxo-ETE to 5-oxo-8,11,14-eicosatrienoic acid (5-oxo-ETrE) by eicosanoid ⁶-reductase results in a 1000-fold reduction in potency [12]. 5-Oxo-ETrE can be further metabolized to 18- and 19- hydroxy-ETrEs by mouse macrophages [95].

4.1.3. 5-oxo-ETE receptor and intracellular signalling—It was obvious from the initial studies on 5-oxo-ETE that its actions are mediated by a highly selective receptor. As discussed above, minor structural changes can nearly abolish its biological activity. Moreover, the actions of 5-oxo-ETE are blocked by homologous desensitization induced by 5-oxo-ETE or closely related ligands, but are not subject to heterologous desensitization by other ligands [191]. Furthermore, cellular responses to 5-oxo-ETE are blocked by inactivation of Gα_{i/o} with pertussis toxin, indicating that its actions are mediated by a G protein-coupled receptor (GPCR) [158,162,195]. Studies on the specific binding of 5-oxo-ETE were initially complicated by its rapid uptake into cellular lipids. However, when esterification was blocked using the fatty acyl CoA synthetase inhibitor triacsin C, 5-oxo-ETE was shown to be selectively bound by neutrophil membranes with a K_d of 4 nM [166].

The receptor for 5-oxo-ETE was cloned by three independent groups who screened libraries of potential ligands for binding to orphan receptors. Hosoi et al [102] identified an intronless sequence in chromosome 2p21 and showed it to encode a 423 amino acid protein that selectively bound 5-oxo-ETE. Takeda et al [233] and Jones et al [113] also identified this sequence, which they codenamed hGPCR48 and R527, respectively. This receptor is highly selective for 5-oxo-ETE, displaying considerably lower affinity for 5-HpETE and only very modest affinity for 5SHETE. It is now known as the OXE receptor and is encoded by the *OXER1* gene [6]. OXE receptor mRNA is highly expressed in peripheral leukocytes, spleen, lung, liver and kidney [102]. Among leukocytes OXE mRNA is most highly expressed in eosinophils > neutrophils > bronchoalveolar macrophages [113]. It has also been found in

basophils [108,229], monocytes [229], a variety of cancer cell lines [164,230] and recently in an adrenocortical cell line [42].

In addition to humans and other primates, *OXER1* orthologs can be found in various mammalian species, including dogs, cats, cows, sheep, elephants, pandas, opossums, and ferrets. Several species of fish, including the zebrafish as discussed in section 4.1.1, above also have *OXER1* orthologs. However, an *OXER1* ortholog is absent in mice and other rodents, which has impeded progress in our understanding of the physiological and pathophysiological roles of 5-oxo-ETE.

As noted above, the OXE receptor signals primarily through a G_i protein, as most of its actions can be blocked by pertussis toxin. Although 5-oxo-ETE can inhibit adenylyl cyclase through α_i , this does not appear to contribute to its chemoattractant effects on eosinophils and neutrophils as demonstrated by the use of the biased antagonist Gue1654. This compound prevents $\beta\gamma$ -mediated OXE signalling [13] and recruitment of β -arrestin [120], and blocks the effects of 5-oxo-ETE on calcium mobilization, actin polymerization, cell migration and adhesion to endothelial cells, and the respiratory burst but has no effect on 5-oxo-ETE-mediated inhibition of adenylyl cyclase. Thus the actions of 5-oxo-ETE on granulocytes are mediated by $G\beta\gamma$ and possibly by β -arrestin rather than by $G\alpha_i$.

Following activation of $G\beta\gamma$ 5-oxo-ETE rapidly mobilizes intracellular calcium by activation of phospholipase C, resulting in the release of IP_3 and diacylglycerol [103]. There is also evidence for the participation of various PKC isoforms in the response to 5-oxo-ETE, including PLC- δ , PKC- ζ [126], and PKC- ϵ [204]. 5-Oxo-ETE also stimulates the phosphorylation of MAP kinases, including ERK-1, ERK-2 [103,126,162,163], and p38 [126,208]. Activation of ERK leads to phosphorylation of cPLA₂ and release of AA [162,250].

4.1.4. OXE receptor antagonists—The first compounds to be identified as 5-oxo-ETE antagonists were the 12-lipoxygenase-generated metabolites 5-oxo-ETE, 5-oxo-12S-HETE and its 8-trans isomer, which inhibited 5-oxo-ETE-induced calcium mobilization in neutrophils with IC₅₀ values of 0.5 and 2.5 μ M, respectively (Fig. 6) [190]. Although these substances would not be suitable as drugs due to their instability and metabolism, they encouraged us to chemically synthesize a series of compounds containing groups similar to the portions of 5-oxo-ETE essential for biological activity attached to an indole scaffold. In compound **346**, 5-oxovalerate and hexyl groups mimicking respectively the C₁₋₅ and terminal hydrophobic regions, which we had previously shown to be critical for the biological activity of 5-oxo-ETE [174], were placed on a 6-chloroindole scaffold (Fig. 6). **346** was devoid of agonist activity and inhibited the effects of 5-oxo-ETE on calcium mobilization in neutrophils with an IC₅₀ (400 nM) similar to that of 5-oxo-12S-HETE [72]. After testing various modifications of **346** we found that addition of a methyl group to the 3-position of the 5-oxovalerate chain dramatically increased potency [71]. This compound is a racemic mixture of two enantiomers, separation of which by chiral-HPLC revealed that the biological activity resides almost exclusively in a single enantiomer. We were able to synthesize both enantiomers by chiral synthesis [175] and found the S-enantiomer (i.e. **S-264**) was the one with potent antagonist activity (Fig. 6). We also developed a second

series of compounds in which acyl and hexyl groups were present in the 3- and 2- positions of 5-chloro-1-methylindole. The most potent of these is the *S*-enantiomer of **230**. The IC₅₀ values for inhibition of calcium mobilization by *S*-**230** and *S*-**264** are about 6 nM. Both compounds also block actin polymerization and cell migration in response to 5-oxo-ETE. They are highly selective for the OXE receptor and do not affect the response to a variety of other proinflammatory mediators. Preliminary pharmacokinetic experiments indicate that both compounds appear rapidly in the blood after oral administration (unpublished work). We have continued to examine the effects of different modifications on antagonist activity and have recently identified compounds that are considerably more potent than those described above (unpublished work).

There is one other OXE receptor antagonist that has recently been reported and referred to above (Section 4.1.3). The benzobisthiazole antagonist Gue1654 blocks 5-oxo-ETE-induced activation of neutrophils and eosinophils [13,120]. When compared to **230** and **264** we found it to be less potent, with an IC₅₀ of about 300 nM [71].

4.1.5. 5-Oxo-ETE in asthma and eosinophilic disorders—At the same time that we reported the 5-HEDH-catalyzed formation of 5-oxo-ETE by neutrophils, Schröder identified 5-oxo-15S-HETE as a product of AA metabolism by soybean lipoxygenase with potent eosinophil chemoattractant activity [210]. We found that 5-oxo-ETE and 5-oxo-15S-HETE activate neutrophils by the same mechanism, as they cross-desensitize to one another but do not affect the responses of neutrophils to other chemoattractants [191]. 5-Oxo-ETE elicits a variety of other responses in eosinophils similar to its effects on neutrophils (Fig. 7). It induces the rapid mobilization of intracellular calcium and actin polymerization, promotes the surface expression of both CD11b [45,188,211] and the leukocyte activation marker CD69 [240], and stimulates the shedding of L-selectin [188]. It also triggers the respiratory burst in eosinophils [45] and the release of the granule enzymes β -glucuronidase, eosinophil peroxidase and arylsulfatase [163].

Among lipid mediators 5-oxo-ETE is the most powerful eosinophil chemoattractant. At low concentrations it induces a response similar to PGD₂, but at higher concentrations it elicits a much stronger response [143]. It is also more potent than PAF and 5-oxo-15S-HETE [163,187]. LTB₄ and cysLTs have negligible chemoattractant effects on human eosinophils, despite the potent effects of LTB₄ on guinea pig eosinophil migration [213]. As well as having direct chemoattractant effects on eosinophils, 5-oxo-ETE acts synergistically with other proinflammatory mediators, including PAF [187], eotaxin, and RANTES, to promote eosinophil migration [186]. GM-CSF strongly enhances 5-oxo-ETE-induced eosinophil degranulation and synergistic interactions also exist with a number of other proinflammatory mediators, resulting in increased release of granule enzymes [163].

5-Oxo-ETE does not appear to have a direct effect on eosinophil survival. However, when incubated with cocultures of eosinophils and monocytes or when conditioned medium from monocytes cultured in the presence of 5-oxo-ETE is added to eosinophils, the survival of these cells is prolonged substantially [224]. We found that 5-oxo-ETE stimulates the release of GM-CSF from monocytes and that the prosurvival effect of conditioned medium from 5-oxo-ETE-treated monocytes could be blocked by an antibody against GM-CSF (Fig. 7). The

ability of 5-oxo-ETE to elicit the release of GM-CSF has additional implications in that this cytokine has been shown to increase the production of 5-LO products (and therefore presumably 5-oxo-ETE) from neutrophils [48,183,184] and also to strongly enhance the response of eosinophils to 5-oxo-ETE as discussed above. In addition to its effects on GM-CSF release, 5-oxo-ETE also has direct chemoattractant effects on monocytes and acts synergistically with other monocyte chemoattractants such as MCP-1 and MCP-3 resulting in increased chemotactic responses [223]. 5-Oxo-ETE promotes the passage of eosinophils across the basement membrane [77] and is a powerful inducer of migration of these cells across endothelial cell monolayers [46]. This is due not only to its chemoattractant effect, but also to the activation of protease pathways. It stimulates the passage of eosinophils through artificial Matrigel basement membranes [77] by inducing the release of MMP-9 and increasing the expression of both MMP-9 and the urokinase-type plasminogen activator receptor (uPAR) [126,127]. This results in degradation of components of the matrix, permitting the passage of eosinophils. These findings were confirmed by the inhibition of this response by antibodies against MMP-9 and uPAR and as well as by the use of a metalloproteinase inhibitor [77].

We found that 5-oxo-ETE induces a robust infiltration of eosinophils into human skin following intradermal injection [147]. This response was observed 6 and 24 h after injection and was considerably greater in asthmatic subjects compared to controls. There were also modest increases in neutrophil and macrophage numbers, but these did not differ between asthmatic and control subjects. This study demonstrates the activity of 5-oxo-ETE as an *in vivo* eosinophil chemoattractant in humans and suggests that this substance could be an important mediator in eosinophilic disorders such as asthma.

4.1.6. 5-Oxo-ETE and cancer—Based on prior epidemiological studies linking high fat diets to cancer [203], Ghosh and Myers set out to determine whether this could be due to the generation of metabolites of AA. They found that AA stimulates the proliferation of both androgen-independent PC3 cells and androgen-dependent LNCaP cells, both derived from prostate cancers [69]. This effect was blocked by 5-LO and FLAP inhibitors but not by inhibitors of COX-1/2, 12-LO, or cytochrome P450, suggesting that it was mediated by a 5-LO product. This is consistent with other studies demonstrating that 5-LO pathway inhibitors induce apoptosis in tumor cells derived from a variety of tissues [5,51,70,84] and reduce tumor development in animal models [144,200]. The stimulatory effect of AA on prostate tumor cell proliferation was mimicked by 5-oxo-ETE and to a lesser extent by 5S-HETE, but not by leukotrienes B₄, C₄, or D₄. Furthermore, 5-oxo-ETE blocked the pro-apoptotic effect of the FLAP inhibitor MK-886 [70] and inhibited selenium-induced apoptosis in prostate cancer cells [68]. It also increased the rates of proliferation of cancer cells derived from a variety of other tissues [164].

Cancer cells have been reported to synthesize 5-HETE [70,79,89] and we have shown that a variety of cancer cell lines contain high levels of 5-HEDH and can convert inflammatory cell-derived 5S-HETE to 5-oxo-ETE, especially when the cells are stressed [75]. Human malignant pleural mesothelial cells but not normal mesothelial cells have been reported to express 5-LO and to synthesize 5S-HETE [202]. As with prostate cancer cells, 5-LO inhibitors or siRNA against 5-LO induced apoptosis in these cells, which could be prevented

by addition of 5S-HETE. This growth-promoting effect appeared to be mediated by induction of the synthesis of VEGF, which is an endogenous growth factor for malignant mesothelial cells. In view of the wide distribution of 5-HEDH, it seems probable that the effects of 5S-HETE in this study could have been mediated by 5-oxo-EETE.

The proliferative effects of 5-oxo-EETE on prostate cancer cells appear to be mediated by activation of PLC- β , resulting in the release of diacyl glycerol and activation of PKC- ϵ [204,205]. Consistent with these findings, the OXE receptor is expressed in a variety of tumor cell lines from different sources [164], including prostate tumors [230]. Knockdown of this receptor using siRNA was found to reduce the viability of PC3 cells [230], raising the possibility that OXE receptor antagonists could be useful in the treatment of cancer.

4.2. Biological actions of 12S-HETE, 12-oxo-EETE and related products

4.2.1. Role of 12S-HETE in thrombogenesis—Although 12-lipoxygenase and its principal product 12S-HETE were discovered in platelets in 1974 [83], defining the precise role for this substance in regulating platelet function has been challenging [255]. There is evidence that 12S-HETE can inhibit TXA₂-induced platelet aggregation [43] as well as the binding of TP receptor ligands [63]. However, studies utilizing mice lacking 12-LO as well as selective 12-LO inhibitors have not given consistent results as to whether 12-LO and its product 12S-HETE play a direct physiological role in stimulating [112] or inhibiting [254] platelet aggregation. Nevertheless, 12S-HETE appears to regulate some aspects of platelet function, including increased surface expression of the adhesion molecule P-selectin [171]. 12S-HETE has been shown promote the expression of tissue factor from monocytes in the presence of either P-selectin [177] or LPS [136], and could thereby contribute to thrombogenesis in this manner.

Another way in which 12S-HETE could promote thrombogenesis is by activating platelet NADPH oxidase, resulting in the generation of superoxide, which inhibits the metabolism of ADP and scavenges NO [59]. 12S-HETE may be an important mediator of HIV-related thrombocytopenia through a similar mechanism [152]. This condition is associated with high levels of antiplatelet integrin GPIIb antibodies, which activate platelet NADPH oxidase by stimulating the synthesis of 12S-HETE, ultimately resulting in reactive oxygen species-mediated destruction of platelets.

4.2.2. 12S-HETE receptor—Binding sites selective for 12S-HETE were first described in human squamous cell carcinoma cells [76] and later in murine Lewis lung carcinoma cells [93]. The latter high affinity binding sites (K_d , 0.5 nM) were found to exist as a 50 kDa subunit within a 650 kDa cytosolic complex that also includes the heat shock proteins hsp70 and hsp90 and has been shown to occur in several cancer cell lines as well as in human platelets [94]. The 12S-HETE binding subunit dissociates from the complex in the presence of ATP and binds to NCOA1 (nuclear receptor coactivator-1) in the presence of 12S-HETE [125], suggesting that it may have a role in regulating gene transcription in the nucleus.

12S-HETE can also act through a GPCR. When added to murine melanoma cells it triggered rapid increases in the intracellular levels of IP₃ and diacyl glycerol coupled with the translocation of PKC- α to the plasma membrane [133]. These intracellular responses were

associated with increased cellular adhesion to fibronectin and were blocked by the G_i protein inhibitor pertussis toxin, indicating the involvement of a GPCR. Pertussis toxin was also shown to block the MAP kinase-dependent growth promoting effects of 12S-HETE on fibroblasts [156]. Consistent with these findings, high affinity binding sites (K_d , 1 nM) selective for 12S-HETE were detected on melanoma cells [133]. Although other HETEs did not compete, 12S-HETE binding was inhibited by low concentrations (IC_{50} , 4 nM) of 13-HODE, the product of linoleic acid metabolism by 15-LO-1 [133]. 13S-HODE, as well as PKC inhibitors, also inhibited 12S-HETE-induced tumor cell adhesion to fibronectin, suggesting that 13S-HODE may act as a 12S-HETE antagonist and thereby protect against tumor cell metastasis. The orphan GPCR GPR31 has recently been identified as a receptor for 12S-HETE [78]. The cloned receptor displayed high affinity for 12SHETE (K_d , 5 nM) and had much lower affinities for other HETE isomers. Interaction of this receptor with 12S-HETE was associated with activation of ERK1, ERK2, MEK, and NF- κ B. Knockdown of the 12S-HETE receptor blocked the stimulatory effect of 12S-HETE on the migration of tumor cells through Matrigel [78].

4.2.3. 12S-HETE and cancer—There is considerable evidence that 12S-HETE promotes cancer due to its effects on both tumor cells and endothelial cells, resulting in increased tumor growth and metastasis. Tumor cells express 12-LO at higher levels than normal cells and can synthesize 12S-HETE. [179]. Inhibition of 12-LO using enzyme inhibitors or downregulation with siRNA resulted in cell cycle arrest and apoptosis that were associated with increased caspase activity and reduced levels of pro-survival Bcl proteins [178]. These effects could be prevented by treatment with 12S-HETE. Another mechanism whereby 12S-HETE can increase cell survival was shown to be through enhanced expression of the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ [180]. Overexpression of 12-LO in these cells had similar effects to addition of exogenous 12S-HETE, and these effects could be blocked by inhibitors of this enzyme such as baicalein.

In addition to promoting tumor cell survival, 12S-HETE has a variety of effects, both directly on tumor cells as well as on endothelial cells, that favor tumor metastasis. 12S-HETE induces PKC-dependent cytoskeletal rearrangements in tumor cells resulting in increased motility [237]. It also acts on tumor cells to elicit the release of cathepsin B, which can contribute to degradation of the subendothelial basement membrane and thereby promote metastasis by enhancing the passage of tumor cells in and out of the bloodstream [101]. Overexpression of 12-LO in tumor cells increases their adhesiveness to matrix components and their metastasis to bone in vivo [154]. Furthermore, addition of 12S-HETE or overexpression of 12-LO in prostate tumor cells stimulates the release of the metalloproteinase MMP-9, which plays an important role in the onset of tumor angiogenesis [47]. 12S-HETE also increased the release of another proangiogenic molecule, VEGF, from prostate tumor cells, whereas 12-LO inhibitors had the opposite effect, suggesting that 12S-HETE is an endogenous regulator of VEGF secretion by these cells [153]. Overexpression of 12-LO had a similar effect [141,153].

In addition to its direct effects on tumor cells 12S-HETE can also promote metastasis by directly activating endothelial cells. When cocultured with endothelial cells tumor cells release 12SHETE, which acts on endothelial cells to induce PKC-dependent cytoskeletal

rearrangement and cell retraction [100]. This exposes the subendothelial matrix, to which tumor cells can readily adhere and migrate into the underlying tissue. 12S-HETE generated by breast cancer cells was shown to play an important role in their transmigration across lymphatic endothelial cells. MCF-7 cell spheroids induce local disruptions in lymphatic endothelial cell monolayers, permitting their transmigration. This can be prevented by blocking 12S-HETE formation by MCF-7 cells using pharmacological inhibitors or treatment with sh-RNA [117]. 12S-HETE appears to act by inhibiting VE-cadherin expression by endothelial cells [241]. Knocking down 12S-HETE synthesis in MCF-7 cells was found to dramatically reduce lymph node metastasis in xenografted tumors in mice [117]. 12S-HETE produced by endothelial cells also appears to play a role in regulating angiogenesis [155]. Selective 12-LO inhibitors reduced endothelial cell proliferation, migration, and tube formation in vitro and attenuated angiogenesis in vivo in a Matrigel plug assay.

4.2.4. 12S-HETE and diabetes—There is evidence that 12S-HETE may play a role in mediating some of the proinflammatory and proapoptotic effects of certain cytokines known to be involved in diabetes. IL-1, in conjunction with TNF α and IFN γ , induces NADPH oxidase-1 (NOX-1) expression in pancreatic islets, resulting in increased levels of reactive oxygen species, caspase 3 activation, and cell death, accompanied by a reduction in glucose-stimulated insulin secretion [248]. These effects were blocked in human INS-1 β -cells by the selective 12S-LO inhibitor NCTT-956, implicating 12SHETE as a mediator of the responses to these cytokines. In agreement with this, 12S-HETE was found to have effects similar to the above cytokines in inhibiting insulin secretion in response to glucose and inducing NOX-1 expression and cell death in islets [138,248]. Moreover, IL-1 β increased mRNA and protein levels, as well as activity, of 15-LO-1 (the enzyme responsible for 12S-HETE synthesis in rodents) in rat β -cells [14]. Furthermore, mice lacking 15-LO-1 were resistant to streptozotocin-induced diabetes [15]. Islets from 15-LO-1-deficient mice were also resistant to the inhibitory effect of cytokines on glucose-induced insulin secretion. There is also evidence that 12S-HETE may be involved in Type 2 diabetes, as 15-LO-1-deficient mice fed a high fat diet displayed dramatically reduced adipose tissue inflammation and insulin resistance compared to wild-type mice [212].

4.2.5. Biological effects of other 12-hydroxy and 12-oxo metabolites of arachidonic acid—12R-HETE, which can be formed from AA by the action of cytochrome P450 enzymes or by 12R-LO, was identified in skin from psoriatic lesions [251] and found to induce lymphocyte chemotaxis, in contrast to 12S-HETE, which had virtually no effect [8]. However, 12R-HETE was about 200 times less potent than LTB₄ in eliciting this response. Similarly, we found that 12R-HETE induces calcium mobilization and chemotaxis in neutrophils via the BLT₁ receptor [194]. It is about 20 times more potent than 12S-HETE, but is less potent than LTB₄ by about 2–3 orders of magnitude. 12R-HETE has also been reported to activate the aryl hydrocarbon receptor [35]. Although μ molar concentrations were required to induce this response, other HETEs, including 12S-HETE, 5S-HETE, and 15S-HETE, were ineffective, demonstrating a high degree of selectivity.

12R-HETE may also have a role in the eye, as it inhibits $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity in the cornea [209]. There are conflicting reports in the literature about the chirality of 12-HETE produced by corneal microsomes with different studies finding principally either 12R-HETE [40], 12S-HETE [168,170], or similar amounts of the two [4]. 12R-HETE appears to be formed by cytochrome P450, as its synthesis is increased by various P450 inducers and blocked by P450 inhibitors [4,40]. There is evidence that the isoform involved is cytochrome P450 4B1, a hypoxia-inducible enzyme [140]. On the other hand, 12S-HETE is formed by a microsomal 12-LO in corneal epithelium, with little 12-LO activity being detected in cytosolic fractions from these cells. This 12-LO activity can be induced by growth factors [170], inhibited by lipoxygenase inhibitors, and does not require NADPH [132,168]. The reason for the discrepancies concerning the chirality of microsome-derived 12-HETE is unclear, but could be related to up- or down- regulation of the relevant enzymes under different conditions.

12-Oxo-EETE, which can be formed from AA by a number of different pathways (Fig. 5), was identified as a metabolite of endogenous AA following stimulation of nervous tissue from the marine mollusk, *Aplysia californica* and was found to induce changes in neuron potential in this species similar to those elicited by histamine [181]. A role for 12-oxo-EETE in the release of fetal membranes in cows following delivery has been reported [115]. 12-Oxo-EETE, albeit at a rather high concentration (10 μM), but not 5-oxo-EETE, 15-oxo-EETE or 12S-HETE, induced the detachment of cultured placental fibroblasts, which was thought to be mediated by the activation of metalloproteinases. Moreover, intrajugular injection of 12-oxo-EETE (~6 mg) in cows promoted the release of fetal membranes after induction of delivery with dexamethasone and $\text{PGF}_{2\alpha}$. We [194] and others [160] have investigated the effects of 12-oxo-EETE on neutrophils, but found it to have only very weak effects on calcium mobilization and aggregation in these cells.

12R-HETrE and 12S-HETrE, which are 10,11-dihydro metabolites 12-oxo-EETE, can be formed as shown in Fig. 5 (Section 3.1.2). 12R-HETrE (which has the same configuration at C_{12} as 12SHETE), is synthesized by corneal epithelial cells and induces rapid vasodilation when applied to the rabbit eye [148]. This compound is also a highly potent angiogenic agent, its actions being mediated by activation of $\text{NF-}\kappa\text{B}$ [227] and by the MAP kinase-dependent induction of VEGF [142]. These effects are quite specific for 12R-HETrE, as they are not shared by other closely related AA metabolites, including 12S-HETrE, 12S-HETE, or 12R-HETE, suggesting a selective receptor-mediated mechanism. Consistent with this, high affinity binding sites (K_d , 43 pM) for 12R-HETrE were reported to be present on microvessel endothelial cells [228], although no information about their selectivity was given.

4.3. Biological effects of 15-HETE and 15-oxo-EETE

Airway epithelial cells [107], eosinophils [98,239] and reticulocytes all express high levels of 15-LO-1 and have the ability to synthesize large amounts of 15S-HETE [149], whereas this enzyme can be induced in monocytes with IL-4 [41]. However, the precise physiological roles of 15S-HETE are not entirely clear, in part because 15-lipoxygenases also generate eoxins as well as potent anti-inflammatory mediators, including AA-derived lipoxins and

DHA (docosahexaenoic acid)-derived protectins and D-series resolvins [62,215]. Furthermore, the products formed by 15-LO-1 and 15-LO-2 are different between humans and mice, as shown in Fig. 1. Therefore, a major role for 15-LO-1 in the lungs may be the generation of lipoxins, resolvins, and protectins, which play protective roles in controlling allergic airway inflammation [90,130,131]. Furthermore, in addition to oxidizing AA to 15S-HETE, 15-LO-1 converts linoleic acid to 13S-HODE and can also oxidize esterified PUFA [122]. Nevertheless, there is evidence that 15S-HETE may be involved in regulating vascular smooth muscle and endothelial cell function [27], cell proliferation [207], and inflammation. Binding sites of moderate affinity (~150–450 nM) have been reported in basophil and mast cell lines, but they appear to have only slightly higher affinity for 15S-HETE compared to 12S-HETE [116,242], so their role is unclear.

15S-HETE is produced by blood vessels, but has only modest effects on vascular smooth muscle under normal circumstances, causing contraction at high concentrations [33]. However, under hypoxic conditions 15-LO-1 is induced, giving rise to higher levels of 15S-HETE. Furthermore, 15S-HETE contracts pulmonary artery rings exposed to hypoxic, but not normoxic, environments, suggesting that it may play a role in redistributing blood flow away from regions of poor ventilation [264]. It may also play a role in cardiovascular disease, as atherosclerotic arteries have been shown to produce increased amounts of 15-HETE [92,246] and apo E-deficient mice lacking 15-LO-1 display reduced atherosclerosis [44]. 15S-HETE induces tyrosine phosphorylation of the EGF receptor in vascular smooth muscle cells, which was mediated by oxidative stress due to activation of NADPH oxidase [220]. This resulted in STAT3-dependent increased expression of MCP-1, which elicited vascular smooth muscle cell migration, leading to neointima formation and vascular wall remodelling. 15S-HETE can also contribute to the development of atherosclerotic lesions by disrupting tight junctions between endothelial cells, facilitating monocyte migration into the intima [123].

15S-HETE may also be involved in regulating tumor development, but its precise role has been more difficult to determine than those proposed for 5-oxo-EETE and 12S-HETE. One difficulty has been that 15-LO-1, which in humans produces 15S-HETE and 13S-HODE, in mice produces principally 12S-HETE, which promotes tumor cell proliferation and metastasis as discussed in Section 4.2.3. 15-LO-1 was reported to be overexpressed [109] or underexpressed [110,260] in different human tumors. The roles of its major products, 13S-HODE and 15S-HETE, are uncertain, and may differ according to the particular type of tumor [145], with 13S-HODE usually being attributed a protective effect [129]. 15-LO-2, which is specific for the oxidation of AA to 15S-HETE, is underexpressed in human tumors [217,234] and is generally believed to play a protective role. For example, 15-LO-2 expression is low in prostate tumor cells, whereas transfection of these cells with cDNA for this enzyme reduces cell proliferation [234]. In agreement with this, 15S-HETE inhibits prostate cancer cell cycle progression. On the other hand, 15S-HETE promotes angiogenesis and could thereby favor tumor growth [124]. There is also evidence for an antitumorigenic effect of 15-LO-2 in the mouse, and 8S-HETE, the product of the murine enzyme, causes cell cycle arrest of murine skin carcinoma cells [119].

Relatively little is known about the biological effects of 15-oxo-ETE. Activation of monocytes and macrophages elicits the formation of both 15S-HETE and its 15-PGDH-derived metabolite 15-oxo-ETE [249]. 15-Oxo-ETE was found to inhibit the proliferation of endothelial cells, suggesting that it might have an antiangiogenic effect.

4.4. Activation of PPARs by HETEs

Peroxisome proliferator-activated receptors are a group of nuclear receptors that regulate the expression of a variety of genes related to metabolism, energy homeostasis, and inflammation [10]. There are three PPAR isotypes, PPAR α , PPAR δ , and PPAR γ . They are generally regarded to have beneficial effects and are the targets of a number of synthetic activators that are used to treat diabetes, atherosclerosis, and other diseases. Endogenous ligands for PPARs include free fatty acids, HETEs, oxo-ETEs, and other eicosanoids, notably 15-deoxy-^{12,14}-PGJ₂.

There is evidence that PPAR γ plays a protective role in at least some types of cancer [199] and the anti-proliferative effects of 15S-HETE on cancer cells are often attributed to its activation of this PPAR [218]. However, the concentrations of HETEs required to activate PPAR γ are often quite high (10–30 μ M), placing some uncertainty as to the pathophysiological relevance of these findings. 15S-HETE (20 μ M) activated PPAR γ in transfected CV-1 cells but was considerably less active than 9S-HODE and 13S-HODE [150]. Similarly, both 15S-HETE and 13S-HODE (~30 μ M) activated PPAR γ in macrophages, resulting in increased expression of CD36 [105]. 15S-HETE also activates PPAR γ in A549 alveolar epithelial cells, thereby inducing apoptosis, which may contribute to the pro-apoptotic effect of IL-4 on these cells, as it induces both 15-LO-1 and PPAR γ [216].

Oxo-ETEs appear to be more potent activators of PPAR γ than HETEs, probably because they can undergo Michael addition reactions resulting in the formation of covalent bonds. 5-Oxo-ETE and 15-oxo-ETE activated PPAR γ in transfected Cos-7 cells in the 1–10 μ M range [219]. 5S-HETE displayed only modest activity at these concentrations, whereas 15S-HETE was inactive. The oxo-ETEs appeared to act by covalently binding a cysteine residue within the ligand binding pocket. 5-Oxo-ETE also activates PPAR γ in MDA-MB-231 breast cancer cells, but only at concentrations in excess of 10 μ M, many orders of magnitude higher than those required for activation of the selective OXE receptor [164]. 5-Oxo-ETE and 12-oxo-ETE were also shown to activate PPAR γ in human sebocytes [49]. Esterified monooxygenated fatty acids also activate PPAR γ . 15-HETE-PE and 15-oxo-ETE-PE both activated PPAR γ in macrophages in the low μ M range (1–2.5 μ M), with 15-oxo-ETE-PE being somewhat more potent [86].

HETEs can also activate PPAR α , which plays an important role in regulating lipid metabolism and is involved in cardiovascular disease and diabetes [65]. The murine 15-LO-2 product 8SHETE is a potent activator of PPAR α , eliciting a strong response at a concentration of 1 μ M [258]. Other HETEs, including 8R-HETE, 5S-HETE, 11S-HETE, 12S-HETE, and 15S-HETE had only weak or negligible effects at this concentration. 8S-HETE was also shown to activate PPAR α in murine keratinocytes and to induce differentiation and keratin expression in these cells [146]. Although the human 15-LO-2

product 15S-HETE does not activate PPAR α , its glyceryl ester does activate this PPAR in the concentration range of 1–10 μ M [121].

5. Conclusions

HETEs and oxo-ETEs are produced by many cell types by a variety of mechanisms. Although they may often be regarded as merely by-products in the formation of more complex eicosanoids such as leukotrienes and prostaglandins, it is clear that at least some of them have their own distinct actions and pathophysiological roles. Although the high concentrations required to elicit responses to these compounds in some cases is of concern, it is possible that in certain specific circumstances high levels of HETEs could be generated. For example, platelets contain particularly high levels of 12-LO and high levels of 15-LO-1 can be induced in epithelial cells and macrophages exposed to IL-4. The existence of a selective receptor has been firmly established for only one member of this group of eicosanoids (5-oxo-ETE), whereas strong evidence exists for one other receptor (12S-HETE). Many HETEs and oxo-ETEs can activate PPARs, but the high concentrations that are often required makes it difficult to evaluate the physiological relevance of this, with the exception of 8S-HETE, which is a potent activator of murine PPAR α . In general, oxo-ETEs appear to be more potent than HETEs in activating PPARs, probably because of their ability to form Michael addition products with these proteins. Many studies implicate HETEs and oxo-ETEs in cancer. The role of 12S-HETE is most firmly established, as it has both direct proliferative effects on tumor cells and can promote tumor metastasis and growth due to its effects on endothelial cells. 5-Oxo-ETE may also promote the development of tumors due to its direct proliferative effects on cancer cells. There is evidence that 15S-HETE may be protective against cancer, but this is not a universal finding, and may depend on the particular type of tumor in question. 5-Oxo-ETE, which is synthesized by a highly selective dehydrogenase, is a potent eosinophil chemoattractant and may play an important role in asthma and other eosinophilic diseases. Research in this area has been hampered by the absence of OXE receptor orthologs in rodents, but the recent availability of potent and selective receptor antagonists may help to define more clearly the pathophysiological role of 5-oxo-ETE.

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Abbreviations

12-HEDH	12-hydroxyeicosanoid dehydrogenase
12-HETrE	12-hydroxy-5,8,14-eicosatrienoic acid

12-HHT	12-hydroxy-5,8,10-hydroxyheptadecatrienoic acid
12-oxo-ETrE	12-oxo-6,8,14-eicosatrienoic acid
13-HODE	13S-hydroxy-9,11-octadecadienoic acid
15-PGDH	15-hydroxyprostaglandin dehydrogenase
5-HEDH	5-hydroxyeicosanoid dehydrogenase
5-oxo-ETrE	5-oxo-8,11,14-eicosatrienoic acid
AA	arachidonic acid
COX	cyclooxygenase
FLAP	5-lipoxygenase activating protein
FOG₇	5-oxo-7-glutathionyl-8,11,14-eicosatrienoic acid
HETE	monohydroxyeicosatetraenoic acids
HpETE	monohydroperoxyeicosatetraenoic acids
LO	lipoxygenase
LT	leukotriene
LX	lipoxin
NCOA1	nuclear receptor coactivator-1
NOX-1	NADPH oxidase-1
oxo-ETE	oxoeicosatetraenoic acids
PAF	platelet-activating factor
PC	phosphatidylcholine
PE	phosphatidylethanolamine
PG	prostaglandin
PPAR	peroxisome proliferator-activated receptor
PUFA	polyunsaturated fatty acid
TX	thromboxane
uPAR	plasminogen activator receptor

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Highlights

- HETEs are AA metabolites formed by lipoxygenases, cyclooxygenases, and P450 enzymes
- Oxo-ETEs are formed from HETEs by specific dehydrogenases
- Receptors have been identified for 5-oxo-ETE (OXE receptor) and 12S-HETE
- 5-Oxo-ETE is an eosinophil chemoattractant that may be involved in asthma and allergy
- 12S-HETE promotes tumor cell proliferation and may be involved in cancer and diabetes

Figure 1. Lipoxygenase, cyclooxygenase and dehydrogenase pathways for the formation of HETEs, oxo-ETEs, and related eicosanoids

*Platelet-type 12-LO; **Leukocyte-type 12-LO or 12/15-LO; ***Generated from aspirin-acetylated COX-2; h, human; m, mouse; p, pig.

Figure 2. Biosynthesis of HpETEs, HETEs, and oxo-ETEs from AA by lipoxygenase and cyclooxygenase pathways
 Lipoxygenases and cyclooxygenases introduce oxygen at one end of an activated 1,4-pentadiene system to give an HpETE, which is reduced by a peroxidase to the corresponding HETE. Oxo-ETEs can be formed by dehydrogenase-catalyzed oxidation of HETEs or by dehydration of HpETEs.

Figure 3. Biosynthesis and metabolism of 5-oxo-EETE

5-Oxo-EETE is formed by oxidation of 5S-HETE by 5-HEDH and metabolized by lipoxygenases, LTC₄ synthase (LTC₄ S), eicosanoid ⁶-reductase (⁶-red), and probably LTB₄ 20-hydroxylase (LTB₄ 20h), to products with lower biological activities.

Figure 4. Regulation of 5-oxo-EETE formation

Synthesis of 5-oxo-EETE by 5-HEDH is critically dependent on intracellular NADP^+ levels. The graph (upper left) shows the relative changes in intracellular NADP^+ concentrations and rates of 5-oxo-EETE synthesis after addition of t-butyl hydroperoxide (100 μM) to U937 cells (cf. ref. 46). NADP^+ levels are elevated, accompanied by increased 5-oxo-EETE synthesis, following activation of the respiratory burst and in conditions of oxidative stress and cell death.

Figure 5. Biosynthesis of 12-HETE, 12-oxo-EET, and 10,11-dihydro metabolites by lipoxygenase and cytochrome P450 pathways

12R-HETE can be formed directly by cytochrome P450 enzymes or from lipoxygenase-generated 12R-HpETE. 12S-HETE is formed from lipoxygenase-derived 12S-HpETE. 12-Oxo-EET can be formed either by oxidation of 12-HETE by 12-HEDH or by dehydration of 12-HpETE. HETrEs are formed from 12-oxo-EET by the successive actions of a ¹⁰-reductase (Δ¹⁰-red) and a 12-ketoreductase (KR).

Figure 6. 5-Oxo-EETE antagonists

Concentration-response curves for the inhibition of 5-oxo-EETE-induced calcium mobilization in human neutrophils by OXE receptor antagonists. Data are from refs 60, 61, and 169.

Figure 7. Effects of 5-oxo-EETE on eosinophils and monocytes

5-Oxo-EETE activates eosinophils by binding to the OXE receptor, which is followed by various responses mediated by $G\gamma\beta$. 5-Oxo-EETE acts on monocytes to induce cell migration as well as the release of the eosinophil survival factor GM-CSF.