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International Union of Pharmacology XLIV. Nomenclature for the Oxoeicosanoid Receptor

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***Abstract*——Oxoeicosanoids are a family of biologically active arachidonic acid derivatives that have been intimately linked with cellular migration. These metabolites are not only potent chemotaxins but also elicit oxygen radical production as well as induce secretory events in different cells. The most potent native ligand reported is 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE), and the cell membrane receptor activated has now been cloned. This receptor is distinct from those receptors activated by either the prostaglandins or the leukotrienes. The purpose of this review is to briefly summarize the molecular evidence and highlight the significance of this receptor. In addition, an official nomenclature for this oxoeicosanoid receptor is proposed.**

I. Overview

The biological responses provoked by arachidonic acid have generally been attributed to the conversion of this substrate to a variety of metabolites. The enzymatic oxidation of arachidonic acid leads to the formation of a family of lipid mediators known as eicosanoids. These products are produced in a well controlled fashion under the direction of specific enzymes (Fig. 1). Modifications in the levels of the metabolites of arachidonic acid have been intimately linked not only with a variety of cellular functions but also with inflammation and disease. In an attempt to understand this modification, one research approach was to isolate and inhibit the enzymes responsible for the formation of specific metabolites. Other investigations were undertaken to characterize and identify the receptors that were activated by the various arachidonic acid products. These efforts have lead to a considerable clarification of the mediator effects and have provided compounds with therapeutic value for patients.

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[1]Abbreviations: 5-LO, 5-lipoxygenase; 5-oxo-ETE, 5-oxo-6,8,11,14-eicosatetraenoic acid; 5-HpETE, 5(*S*)-hydroperoxy-6,8,11,14-eicosatetraenoic acid; 5-HETE, 5(*S*)-hydroxy-6,8,11,14-eicosatetraenoic acid; LT, leukotriene; 5-oxo-15-HETE, 5-oxo-15-hydroxy-6,8,11,13-eicosatetraenoic acid; PMN, polymorphonuclear neutrophil; ECL, eosinophil chemotactic lipid; OXE, oxoeicosanoid; HEK, human embryonic kidney; GPCR, G-protein-coupled receptor; TNFα, tumor necrosis factor α; PAF, platelet-activating factor; CysLT, cysteinyl-leukotriene; GM-CSF, granulocyte macrophage-colony-stimulating factor; [^{35}S]GTPγS, guanosine 5′-*O*-(3-[^{35}S]thio)triphosphate; IUPHAR, International Union of Pharmacology.

Over the last decade a concerted effort to established a nomenclature for the different receptors activated by the eicosanoids has been undertaken (Coleman et al., 1994; Brink et al., 2003). However, due to the complexity of the arachidonic acid cascade, one would expect that other metabolites may activate specific receptors that are different from those previously described. Recently, a receptor (Hosoi et al., 2002; Jones et al., 2003) that is activated specifically by metabolites of the 5-lipoxygenase (5-LO[1]) enzymatic pathway has been reported. These investigators demonstrated that 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE) and related ligands were the principal activators. Therefore, this report outlines how this G-protein-coupled receptor fits into the general class of eicosanoid receptors.

II. Introduction

A considerable amount of evidence has accrued demonstrating that the principal intermediate products in the transformation of arachidonic acid via 5-LO are 5(*S*)-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HpETE), 5(*S*)-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE), and leukotriene A_4 (LTA_4). These molecular entities (Borgeat and Samuelsson, 1979; Stenson and Parker, 1979) are associated with the formation of the leukotrienes and lipoxins. Previous investigations had shown that the cysteinyl-leukotrienes (LTC_4, LTD_4, and LTE_4) were potent contractile agonists of human airway (Buckner et al., 1986) and vascular (Labat et al., 1992) smooth muscles through specific cysteinyl-leukotriene (CysLT) receptor activation. LTB_4 was reported to be a potent proinflammatory agent, due principally to the action on PMNs including chemotaxis and aggregation (Ford-Hutchinson et al., 1980), degranulation (Feinmark et al., 1981; O'Flaherty et al., 1981, 1983), as well as stimulation of adherence to vascular endothelium (Dahlen et al., 1981). These effects are known to occur by activation of BLT receptors. Furthermore, the lipoxins (Serhan, 1994) were shown to be mediators with potent inhibitory actions via specific ALX receptors (Fiore et al., 1992). The 5-LO enzymatic pathway was also reported to be pivotal for the transformation of arachidonic acid to another group of biologically active metabolites, namely, the oxoeicosanoids (Fig. 1).

Morita and coworkers (1990) reported that an eosinophil chemotactic lipid (ECL) was produced by purified human eosinophils in the presence of arachidonic acid. These investigators demonstrated that ECL was not produced by eosinophils in the absence of exogenous arachidonic acid, suggesting that ECL was not preformed but enzymatically synthesized via the 15-lipoxygenase, which was the most abundant arachidonic acid converting enzyme in eosinophils (Turk et al., 1982). Although evidence had demonstrated that cellular migration was induced by LTB_4, several other investigations reported that oxoeicosanoids derived from 5-LO were also capable of inducing chemotaxis both in vitro (Goetzl and Sun, 1979; Goetzl et al., 1980; O'Flaherty et al., 1988; Powell et al., 1992) and in vivo (Yu et al., 1995; Stamatiou et al., 1998; Guilbert et al., 1999). This chemotactic effect was suggested to be associated with activation of a putative receptor that was distinct from BLT receptors. The aim of this presentation is to briefly highlight the observations describing the biological significance of the oxoeicosanoids and to propose a working nomenclature for the recently cloned receptor that is activated by these lipid mediators (Hosoi et al., 2002; Jones et al., 2003).

III. Biosynthesis of Oxoeicosanoids

The transformation of arachidonic acid to the native and potent ligand 5-oxo-ETE associated with cellular migration was principally investigated in isolated blood cells. However, red blood cell membranes were also shown to form this product when appropriately stimulated (Nakamura and Murphy, 1997; Hall and Murphy, 1998). In human PMNs (Powell et al., 1992) a 5(*S*)-hydroxyeicosanoid dehydrogenase pathway was shown to catalyze the formation of 5-oxo-derivatives from two substrates: 1) 12-epi-6-*trans*-LTB_4 and 2) 5-HETE. The data also indicated that human 5(*S*)-hydroxyeicosanoid dehydrogenase had a higher affinity for oxoeicosanoids, such as 5-HETE, which possessed a 5(*S*)-hydroxyl group. This suggested a preferential substrate for 5(*S*)-hydroxyeicosanoid dehydrogenase in human PMN. Recently, Powell and coworkers (1999) showed that platelets also contain 5(*S*)-hydroxyeicosanoid dehydrogenase, which converted 5-HETE to 5-oxo-ETE during cell activation. However, in unstimulated platelets, these investigators observed that 5(*S*)-hydroxyeicosanoid dehydrogenase appeared also to act in a reverse direction by converting 5-oxo-ETE to the less active 5-HETE metabolite. In addition, stimulated platelets converted 5-oxo-ETE to the 12-hydroxy metabolite, 5-oxo-12-HETE, which had been shown to antagonize 5-oxo-ETE-induced calcium mobilization in neutrophils.

These biochemical investigations suggested that the oxoeicosanoid, 5-oxo-ETE, was principally generated from the transformation of 5-HETE via a specific 5(*S*)-hydroxyeicosanoid dehydrogenase. However, Falgueyret and Riendeau (2000) have reported that 5-oxo-ETE can also be formed by a nonenzymatic rearrangement of the allylic epoxide of LTA_4, namely, 5-oxo-ETE, a potent activator of cellular migration. In addition to these two pathways (enzymatic and nonenzymatic) leading to the formation of 5-oxo-ETE, Zarini and Murphy (2003) have suggested the transformation of 5-HpETE to 5-oxo-ETE. This occurred via a cytosol catalytic factor (high molecular weight protein, such as hematin), which facilitated the reaction of 5-HpETE to 5-oxo-ETE through the formation of a 5-alkoxyl radical in murine-elicited macrophages. Therefore, multiple routes have been identified

for the formation of oxoeicosanoids, a group of mediators that possess potent chemotactic properties similar to LTB_4.

A. Cofactors for Oxoeicosanoid Formation

The molecular events associated with the insertion of molecular oxygen at carbon-5 of the arachidonate chain, and the subsequent formation of the specific intermediates mentioned above have been identified in a variety of cells. Under certain conditions, the formation of 5-oxo-ETE often requires cofactors. In human neutrophils the biosynthesis of 5-oxo-ETE has been associated with specific microsomal $NADP^+$-dependent dehydrogenase. This enzyme is responsible for the conversion of 5(*S*)-HETE but not 5(*R*)-HETE (Powell et al., 1992). There is a marked increase in the quantities of 5-oxo-ETE only when neutrophils are pretreated with phorbol myristate acetate (PMA), which elevates $NADP^+$ (Powell et al., 1994). Zhang and coworkers (1996) have also documented a similar dependence on the formation of 5-oxo-ETE in human monocytes and lymphocytes. Monocytes catalyze the conversion of 5-HETE to 5-oxo-ETE via the $NADP^+$ pathway. Lymphocytes can also catalyze the oxidation of arachidonic acid by 5-LO with a variety of

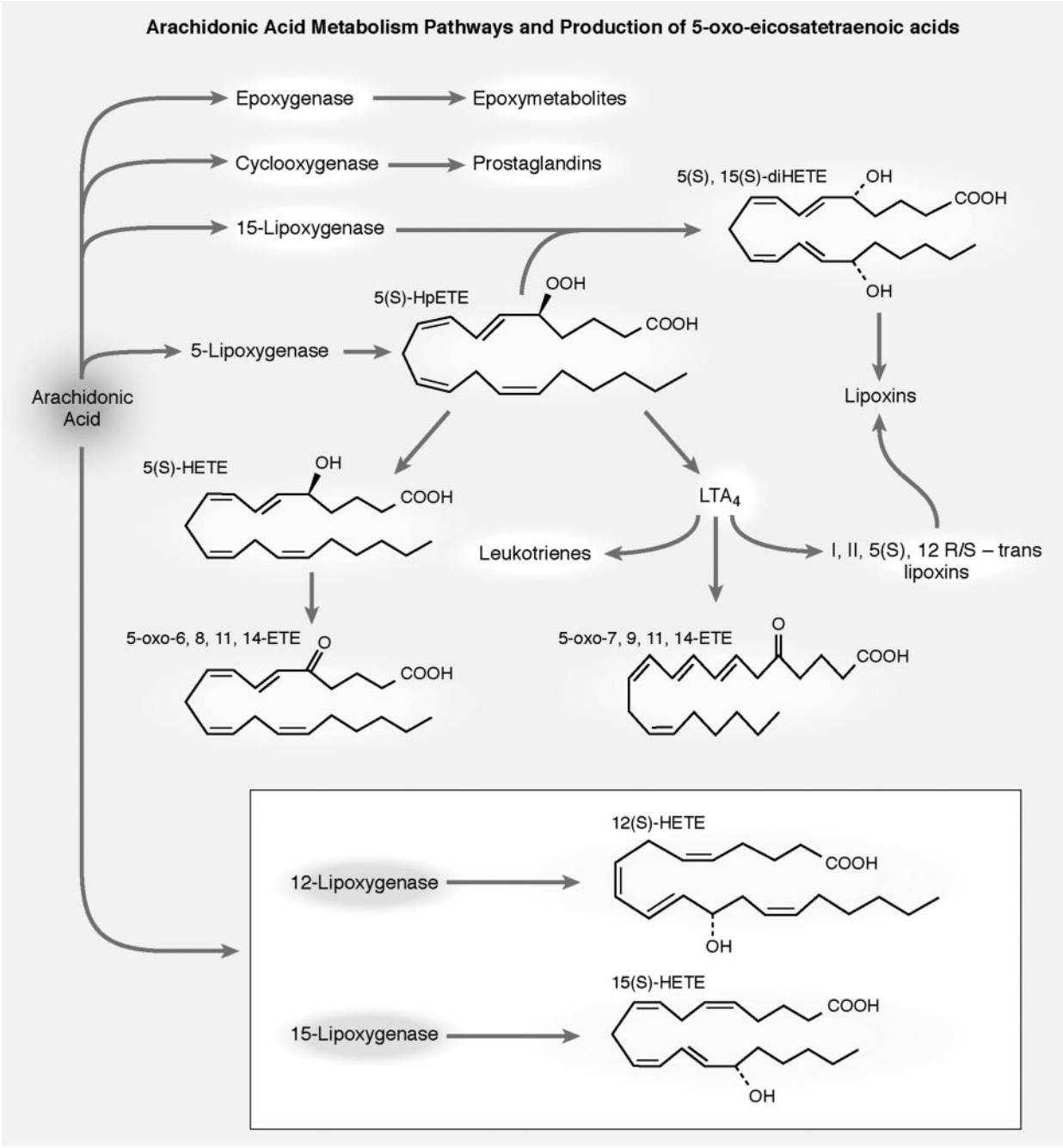

FIG. 1. Arachidonic acid metabolism pathways and production of 5-oxoeicosatraenoic acids. The structures of the principal ligands are presented.

end products identified (Ring et al., 1996, 1997; Werz and Steinhilber, 1996; Bonizzi et al., 1997; Larsson et al., 1998; Werz et al., 2000). In the murine-elicited peritoneal macrophage, 5-oxo-ETE was also detected (Hevko et al., 2001; Heveko and Murphy, 2002). Recently, Zarini and Murphy (2003) demonstrated that in these cells the pathway converts 5HpETE to 5-oxo-ETE by a 5-alkoxy radical intermediate catalyzed by an ferryl-hydroxy complex of hematin in the macrophage cytosol. These data in the elicited macrophage demonstrated that, distinct from neutrophils, 5-HpETE rather than 5-HETE was the precursor for 5-oxo-ETE. Together, these results suggest that not only are there several routes for the production of 5-oxo-ETE, but also the substrates and the cofactors may be different and dependent on the cell studied.

B. Cellular Production of Oxoeicoanoids

Borgeat and coworkers (1976) reported that activation of human neutrophils lead to the release of arachidonic acid and the formation of 5-HETE as well as LTB_4, which was rapidly metabolized to 20-hydroxy-LTB_4. Subsequent work by Powell and coworkers (1984, 1987, 1989, 1992) identified a microsomal dehydrogenase enzyme in PMNs that catalyzed the oxidation of the 5-hydroxy group of 5-HETE containing a 6-*trans* double bond to form 5-oxo-ETE. As mentioned above, this enzyme required $NADP^+$ as a cofactor to convert 5-HETE to 5-oxo-ETE. In addition, Zhang and coworkers (1996) also demonstrated that monocytes contained a dehydrogenase enzyme responsible for the chemical transformation of 5-HETE to 5-oxo-ETE. These studies indicated a controlled enzymatic formation of the 5-oxo-metabolite in several human blood cells. Further studies have shown the formation and release of 5-oxo-ETE in human platelets (Fruteau and Borgeat, 1988; Powell et al., 1999), monocytes (Zhang et al., 1996), eosinophils (Powell et al., 1995a,b), and neutrophils (O'Flaherty and Nishihira, 1987; Powell et al., 1993). Resident mouse peritoneal macrophages were also capable of generating the oxoeicosanoids specifically when challenged with arachidonic acid (Humes et al., 1986). Recently, Zimpher and coworkers (2000) also showed that 5-oxo-ETE was produced by dendritic cells. Although most studies have centered on the cellular production, Kiss and coworkers (2000) reported that the human isolated perfused lung upon challenge with the calcium ionophore (A23187) also released significant levels of 5-oxo-ETE but the exact enzymes involved were not explored. In porcine and rat polymorphonuclear leukocytes, a novel reductase/dehydrogenase pathway distinct from that responsible for the metabolism of prostaglandins had been reported (Powell and Gravelle, 1989). This enzyme was shown to metabolize leukotriene B_4 to 10,11-dihydro-LTB_4 and 10,11-dihydro-12-oxo-LTB_4 and suggested a pathway that converted 6-*trans*-isomers of LTB_4 to dihydro products distinct from that observed in human PMNs (Wainwright et al., 1990). Collectively, these observations suggest that several cells and tissues possess the enzymatic machinery for the coordinated generation of the oxoeicosanoids. Many of these cells also respond to the potent native ligand, 5-oxo-ETE, by an increase in Ca^{2+} mobilization and migration indicating a signal transduction mechanism.

IV. Nomenclature for Oxoeicosanoid Receptors

Following the observation of Morita and coworkers (1990) that a potent ECL was generated by human eosinophils, Schwenk and coworkers (1992) isolated and characterized this 5-LO derivative as 5-oxo-15-hydroxy-6,8,11,13-eicosatetraenoic acid (5-oxo-15-HETE). A number of elegant chemical investigations (Powell et al., 1992; O'Flaherty et al., 1994) demonstrated the presence of an oxo group at the C-5 atom as well as the conjugated *trans-cis* double bonds at positions C-6 and C-8, which were necessary for biological activity. Interestingly, the biological actions of 5-HETE were more closely associated with 5-oxo-ETE than LTB_4 even though the latter mediator also possessed a 5-hydroxyl group. Other structural differences accounted for the differences between 5-oxo-ETE and LTB_4. Specifically, the two conjugated double bonds following the 5-hydroxyl group are *trans-cis* in 5-oxo-ETE, whereas those following the 5-hydroxyl group in LTB_4 are *cis-trans*. In fact the 6-*cis* configuration is necessary for the biological effects of LTB_4 since the 6-*trans*-LTB_4 isomer has been shown to be much less active. Structure-activity studies also showed that a change in the hydroxyl group at C-15 and the oxo group at C-5 in 5-oxo-15-HETE toward 15-oxo-5-HETE lead to complete loss of chemotactic activity. Furthermore, 15-oxo-ETE had no eosinophil chemotactic activity suggesting that the hydroxyl group at C-15 was not pertinent for biological activity. Schwenk and Schroder (1995) also demonstrated that a 5(*S*)-hydroxy group was present instead of an oxo group at C-5 in 5(*S*)-HETE or (5*S*,15*S*)-diHETE, and compared with 5-oxo-ETE, higher concentrations of the former metabolic products were necessary for the chemotactic activities. These data supported the concept that the primary structural requirement of the ligands associated with biological activity were the presence of an oxo group at the C-5 atom. Based on these structure-activity data and the guidelines advanced by the IUPHAR Nomenclature Committee for Leukotriene and Lipoxin Receptors[2], these enti-

[2] IUPHAR Nomenclature Committee for Leukotriene and Lipoxin Receptors: Charles Brink (Chairman), Researcher (CNRS CR-1), CNRS UMR 7131, Hôpital Broussais, Bâtiment Les Mariniers, 96, rue Didot, 75014 Paris, France; Sven-Erik Dahlén, Professor, Unit for Experimental Asthma and Allergy, The National Institute of Environmental Medicine, Karolinska Institutet, S-171 77 Stockholm, Sweden; Jeffrey M. Drazen, Professor of Medicine, Harvard Medical School, Brigham and Woman's Hospital, 75 Francis Street, Boston, MA 02115; Jilly F. Evans, Department of Pharmacology, Merck & Co., WP26A-3000, Sumneytown Pike, P.O. Box 4, West

TABLE 1
The human recombinant oxoeicosanoid receptor

IUPHAR name	OXE
IUPHAR code	2.1:OXE
Alternate names	ECL, 5-oxo-eicosanoid, 5-oxo-ETE, 5-HETE
Amino acid composition	384
Ligand potency	5-oxo-ETE ≫ 5-HpETE > 5-HETE
Selective ligand	None
Gene/chromosome	2p21
Primary coupling	$G\alpha_i$
Primary expression	Northern blot: kidney, liver; RT-PCR: eosinophil, neutrophil, lung macrophage
Accession number (SwissProt)	Q8TDS5

The data are derived from Jones et al., 2003. See text for comparison with the intial publication by Hosoi et al., 2002.

ties may be referred to as oxoeicosanoid (OXE) receptors since the native ligand, 5-oxo-ETE, is the most potent agonist in the cloned receptor assays and the oxo group at C-5 is key for activation of this receptor. Several of these ligand structures are presented in Fig. 1.

V. Molecular Characteristics of Oxoeicosanoid Receptors

In HEK 293 cells transfected with the cDNA of a recently isolated novel G-protein-coupled receptor, Jones and coworkers (2003) indicated that this receptor was activated by 5-oxo-ETE and to a lesser extent by two other closely related ligands, namely, 5-HpETE and 5-HETE. Thus the recombinant receptor had pharmacological properties similar to the putative receptor known to be responsible for chemotaxis in eosinophils (Powell et al., 1995) and neutrophils (O'Flaherty et al., 1994). Of considerable interest was the observation that this receptor was highly expressed on human eosinophils further suggesting that this orphan receptor may be the one described by previous investigators (O'Flaherty et al., 1993; Powell et al., 1995; Sozzani et al., 1996; Zhang et al., 1996). The characteristics of the human recombinant receptor are presented in Table 1. Hosoi and coworkers (2002) reported a rank order potency of 5-oxo-ETE ≫ 5-HpETE > 5-HETE when these ligands were assayed for Ca^{2+} mobilization in Sf9 cells using a GPCR-Gα fusion system. Similar rank order potencies (5-oxo-ETE ≫ 5-HpETE > 5-HETE) were also reported by Jones and coworkers (2003) for Ca^{2+} mobilization. These reports provided evidence for a GPCR polypeptide that was activated selectively by the oxoeicosanoids. However, there were some differences between the two cloned receptors. TG1019 (Hosoi et al., 2002) had an amino acid sequence of 423 with a longer N terminus (39 amino acids) than that reported by Jones and coworkers (2003). These latter investigators apparently had designed their primers to start at the second intiation codon, which is a poorer match to the kozak consensus and less efficient since the −3 position is at a C as opposed to the A at −3 of the first initiation codon. In addition, the sequence (Jones et al., 2003) appears to have three polymerase chain reaction errors relative to the genomic sequence including one amino acid change in the carboxyl terminal. These observations suggest that Jones and coworkers (2003) isolated and studied a

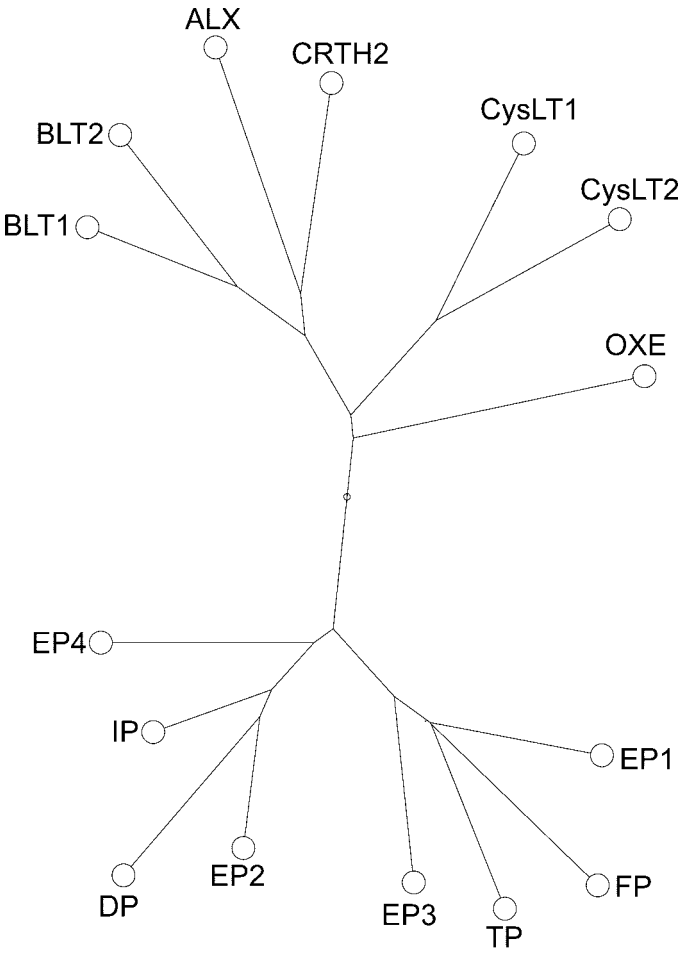

FIG. 2. Dendogram of the GPCRs that are activated by eicosanoids. This evolutionary tree was constructed using the sequences from the prostanoid, leukotriene, and lipoxin receptors. The OXE receptor activated by the potent native ligand, 5-oxo-ETE, is also shown. This phylogenic tree was constructed using the sequences from the receptors and was performed using the "All All. Program" at the Computational Biochemistry Server at ETH Zurich (http://cbrg.inf.ethz.ch/ServerBooklet/chapter2–3.html).

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truncated version of the receptor. However, the ligand potency and tissue expression were similar to the results reported by Hosoi and coworkers (2002). Interestingly, these observations also provided evidence that the N terminus of the receptor played a minor role in ligand-receptor signaling. Hosoi and coworkers (2002) also reported that the TG1019 receptor did not respond to either a variety of prostaglandins or leukotrienes and lipoxins. These data supported the initial observations in eosinophils and PMNs that 5-oxo-ETE activated a putative receptor distinct from the other known eicosanoid receptors.

The phylogenic tree for these different eicosanoid G-protein-coupled receptors is presented in Fig. 2, and the low homology between the chemoattractant and nucleotide receptors are shown in Fig. 3.

VI. Significance of Oxoeicosanoid Receptors

Oxoeicosanoids are a family of biologically active arachidonic acid derivatives that have been initimately linked with cellular migration. These agents are potent chemotaxins for eosinophils (Powell et al., 1995; Schwenk and Schroder, 1995) as well as for PMNs and monocytes (Table 2) via the mobilization of calcium (O'Flaherty et al., 1993; Powell et al., 1993). Other investigations have reported that these mediators may also provoke degranulation particularly in cells that have been primed with cytokines such as TNFα (O'Flaherty et al., 1993, 1996). In addition, there are other effects such as oxygen radical formation subsequent to GM-CSF treatment (O'Flaherty et al., 1996; Czech et al., 1997) as well as increased CDIIb expression

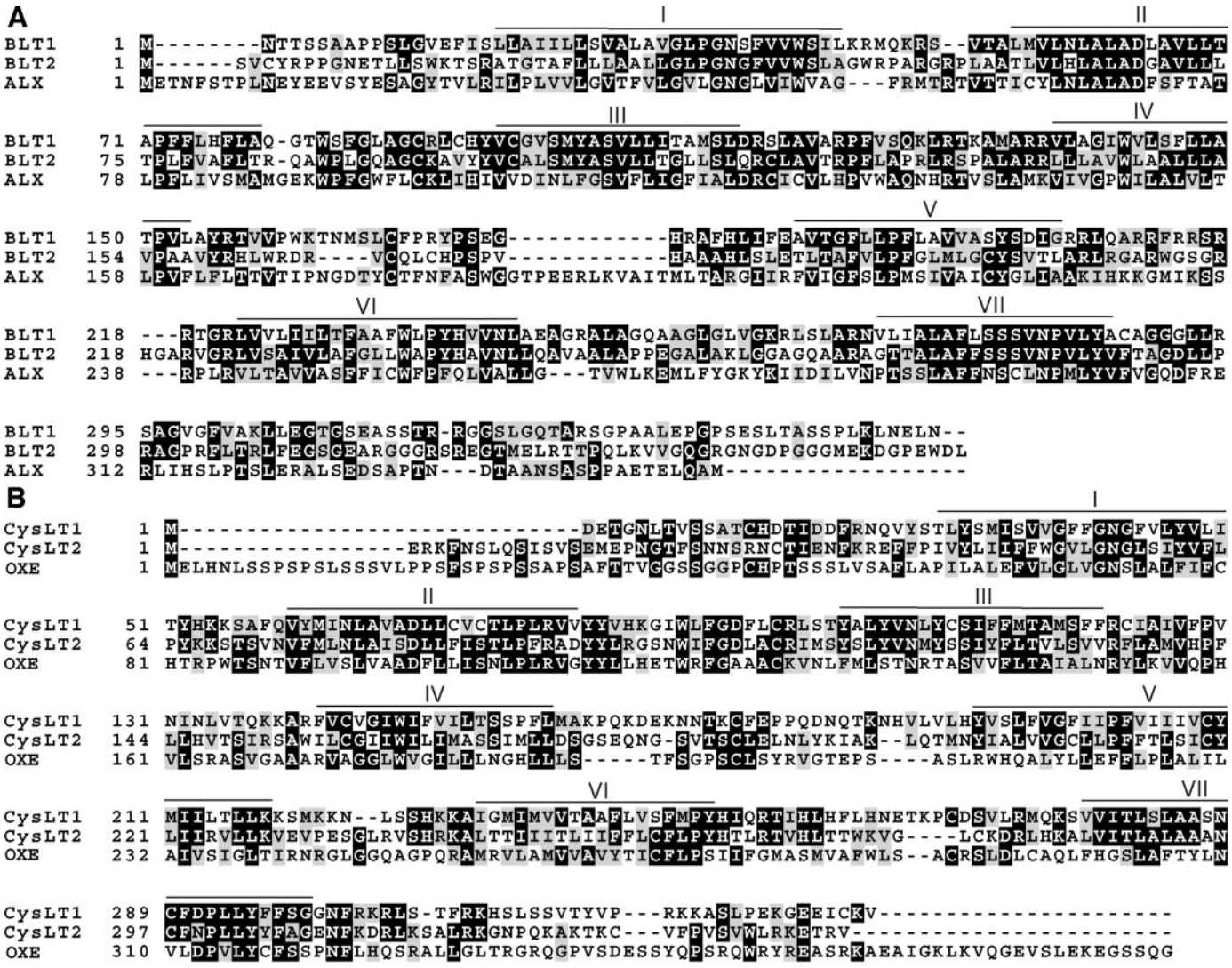

FIG. 3. The sequence alignments of the human leukotriene, lipoxin, and 5-oxoeicosanoid receptors. The sequence alignments of human BLT_1, BLT_2, and ALX receptors (top panel) are shown. ALX shares 27.8% and 27.8% identity with BLT_1 and BLT_2, respectively. The sequence alignments of human $CysLT_1$, $CysLT_2$, and OXE receptors are also presented (bottom panel). OXE shares 23.2% and 25.3% identity with $CysLT_1$ and $CysLT_2$, respectively. The amino acid sequences were aligned using Clustal W and converted using Boxshade 3.21. The putative transmembrane domains of human receptors predicted by Kyte-Doolittle hydrophobicity analysis were lined and labeled as I–VII. These sequence data are available from EMBL/GenBank/DDBJ under the accession numbers D89078 (hBLT1), AB029892 (hBLT2), U81501 (hALX), AF119711 (hCysLT1), AF254664 (hCysLT2), and AAO17739 or NP_683765 (hOXE).

TABLE 2
Biological actions of the oxo-eicosatetraenoic acids

Assay	Assay/Function	Main Ligands	Reference
In vivo			
Intact PMNs (human)	Chemotaxis and calcium mobilization	5-oxo-ETE 5-HETE 15-oxo-hydroxy-ETE, 5-oxo-15-hydroxy-ETE, 5-hydroxy-15-oxo-ETE, 5,15,diHETE, 5-oxo-EPE	O'Flaherty and Nishihira., 1987 O'Flaherty et al.,1988 O'Flaherty et al.,1990 O'Flaherty et al, 1993 Powell et al., 1993 Powell et al., 1995 Powell et al., 1996 O'Flaherty et al., 1993 O'Flaherty et al., 1994 Falgueyret et al., 2000
PMN membranes (human)	^{3}[H]-5-oxo-ETE binding	5-oxo-ETE	O'Flaherty et al., 1998 O'Flaherty et al., 2000
Primed intact PMNs (human) [TNFα, PAF, Cytochalsin B; GM-CSF or G-CSF]	Degranulation (lysozyme, β-glucuronidase, O_2^- production)	5-oxo-ETE 5-HETE	O'Flaherty et al., 1985 O'Flaherty et al., 1993 O'Flaherty and Rossi, 1993 O'Flaherty et al., 1996 Czech et al., 1997
Eosinophils (human)	Chemotaxis and calcium mobilization	5-oxo-ETE 5-oxo-EPE 5-oxo-15-HETE 5-oxo-ETE-methyl ester	Schwenk et al., 1992 Powell et al., 1995 Schwenk and Schröder, 1995 Powell et al., 1995
Monocytes (human)	Chemotaxis	5-oxo-ETE 5-oxo-15-OH- ETE 5-HETE	Sozzani et al., 1996 Zhang et al., 1996
PC3 cells (human prostate)	Cell proliferation (increase)	5-HETE 5-oxo-ETE	O'Flaherty, et al., 2002
Epithelial cells (Guinea-pig jejunum)	Isotonic cell volume (reduction)	5-oxo-ETE 5-HETE	Macleod et al.,1999
In vivo			
Rat (tracheal instillation)	Lung eosinophil chemotaxis	5-oxo-ETE	Yu et al., 1995 Stamatiou et al., 1998

and L-selectin shedding (Powell et al., 1997, 1999). Furthermore, MacLeod and coworkers (1999) demonstrated that 5-oxo-ETE induced secretory events in intestinal epithelial cells, data which confirmed previous observations (Musch et al., 1982).

LTB_4, a potent chemotactic agent, was known to exhibit an array of functions, whereas the 5-oxo-ETE appears to exhibit a limited and specific activity, namely, chemotaxis of eosinophils, PMNs, and monocytes. O'Flaherty and coworkers (1995, 1996) reported that LTB_4 and 5-HETE had similar stimulatory activity in human neutrophils but the latter mediator had little affinity for BLT receptors and was resistant to BLT antagonists. These observations were extended by monitoring ^{3}H-labeled 5-oxo-ETE binding in PMN plasma membranes and demonstrating that specific binding sites for this radiolabel were not effected by other receptor ligands (O'Flaherty et al., 1998, 2000). These results suggested a putative receptor for the oxoeicosanoids with the most potent native ligand being 5-oxo-ETE. Although the other ligands, 5-oxo-15-HETE and 5-HETE, were less potent, they were also shown to activate this same receptor.

In PMNs that were primed with TNFα, O'Flaherty and coworkers (1993) demonstrated that 5-HETE had full agonist activity for eliciting oxygen radical production. In addition, primed PMNs were desensitized to a subsequent 5-HETE challenge but not to other chemotactic factors, such as, PAF or LTB_4 (O'Flaherty et al., 1988). 5-HETE also provoked the hydrolysis of [γ-^{32}P]GTP and bound [^{32}S]GTPγS. These actions were stereoselective and were pertussis toxin-sensitive. Furthermore, in a PMN plasma membrane radioligand binding assay with ^{3}H-labeled 5-oxo-ETE, GTP analogs markedly reduced the binding by disruption of G-proteins and provoked the loss of the high affinity receptor whereas ATPγS had no effect. These observations were compatible with the notion that 5-HETE activated a putative plasma membrane bound receptor, and 5-oxo-ETE was the most active analog (O'Flaherty et al., 1998). In this latter study with PMNs, a K_d of 3.8 nM was reported for 5-oxo-ETE. In other assays, 5-oxo-ETE was shown to inhibit cAMP levels with an IC_{50} value of 0.33 nM in HEK 293 cells (Jones et al., 2003), whereas the value was 33 nM in Chinese hamster ovary cells (Hosoi et al., 2002). When the CysLTs were tested for their activity against the stable R527/HEK Gα 16 cell line, no calcium mobilization activity was observed and a $CysLT_1$ antagonist (iralukast) did not block the 5-oxo-ETE-induced signal (Jones et al., 2003).

LTB_4 has been reported to cause unprimed PMNs to degranulate and produce a significant increase in oxygen radical formation, whereas 5-oxo-ETE did not exhibit this activity. In contrast, both eicosanoids were equi-effective in provoking these responses in "primed" cells but the BLT antagonist, LY255283, blocked only the effects of LTB_4 and not the actions of 5-oxo-ETE. Furthermore, in primed PMNs both ligands, 5-oxo-ETE

and LTB_4, were reported to stimulate secretory vesicle mobilization, mitogen-activated protein kinase activation, and arachidonic acid release (Wijkander et al., 1995; O'Flaherty et al., 1996); however, only the LTB_4 effects were blocked by a BLT antagonist (O'Flaherty et al., 2000). These results suggested that 5-oxo-ETE did not activate BLT receptors. These data also suggested that the putative receptor was found on eosinophils and PMNs and was activated only when there had been a prior cellular receptor activation by other agents. This suggests the presence of a cooperative functional receptor specifically related to chemotaxis since this receptor appears primarily to be activated under conditions where there is an accompanying cellular stimulus, that is, in primed cells. Interestingly, Guilbert and coworkers (1999) have reported no significant differences in the transmigration of eosinophils derived from normal and asthmatic subjects. These data suggest that receptor number and activity may not be altered in this disease. In contrast, Muro and coworkers (2003) demonstrated that 5-oxo-ETE elicited granulocyte infiltration in the skin of asthmatics suggesting that these subjects may be more sensitive to this mediator. However, the appropriate molecular probes may be necessary to confirm these observations and to understand more clearly the potential role of this receptor in normal physiological conditions as well as in pathology.

VII. Conclusion

This brief review is a summary of the data concerning the recently cloned receptor that is activated by several oxoeicosanoids. Since the native most potent ligand is 5-oxo-ETE, this receptor class may be referred to as OXE (oxoeicosanoid receptors). The molecular studies clearly established this receptor as distinct from the other classical eicosanoid types (Coleman et al., 1995; Brink et al., 2003). Additional competition binding studies with geometric isomers and related structures are still required to clarify the nature and selectivity, or lack of, for this receptor. Further investigations must also be undertaken to establish whether or not this receptor can be antagonized by 5-oxo-12-HETE as had been reported in neutrophils. Since this receptor is primarily linked to cell migration the question may be asked as to whether cells transfected with this receptor will also exhibit cellular migration when stimulated with the potent ligands and whether there is cross-desensitization with other ligands such as LTB_4.

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