# Eicosanoids

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Abbreviations used: ARA, arachidonic acid; COX, cyclooxygenase; $cPLA_2$, cytosolic phospholipase $A_2$; cytP450, cytochrome P450; DP, receptor for D-series prostaglandins; EET, epoxyeicosatrienoic acid; EP, receptor for E-series prostaglandins; EPA, eicosapentaenoic acid; FP, receptor for F-series prostaglandins; HETE, hydroxyeicosatetraenoic acid; HpETE, hydroperoxyeicosatetraenoic acid; IP, receptor for I-series prostaglandins; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin; $PLA_2$, phospholipase $A_2$; PPAR, peroxisome proliferator activated receptor; PUFA, polyunsaturated fatty acid; Th1, T helper 1; Th2, T helper 2; TP, receptor for thromboxanes; TX, thromboxane.

**Abstract**

This article describes the pathways of eicosanoid synthesis, eicosanoid receptors, the action of eicosanoids in different physiological systems, the roles of eicosanoids in selected diseases, and the major inhibitors of eicosanoid synthesis and action. Eicosanoids are oxidised derivatives of 20-carbon polyunsaturated fatty acids formed by the cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (cytP450) pathways. Arachidonic acid is the usual substrate for eicosanoid synthesis. The COX pathways form prostaglandins and thromboxanes, the LOX pathways form leukotrienes and lipoxins, and the cytP450 pathways form various epoxy, hydroxy and dihydroxy derivatives. Eicosanoids are highly bioactive acting on many cell types through cell membrane G-protein coupled receptors, although some eicosanoids are also ligands for nuclear receptors. Because they are rapidly catabolised eicosanoids mainly act locally to the site of their production. Many eicosanoids have multiple, sometimes pleiotropic, effects on inflammation and immunity. The most widely studied is prostaglandin $E_2$. Many eicosanoids have roles in the regulation of the vascular, renal, gastrointestinal and female reproductive systems. Despite their vital role in physiology, eicosanoids are often associated with disease, including inflammatory disease and cancer. Inhibitors have been developed that interfere with the synthesis or action of various eicosanoids and some of these are used in disease treatment, especially for inflammation.

## Introduction and scope

Eicosanoids are oxidised derivatives of 20-carbon polyunsaturated fatty acids (PUFAs). Substrate PUFAs are released from cell membrane phospholipids and then metabolised by cyclooxygenase (COX), lipoxygenase (LOX) or cytochrome P450 oxidase (cytP450) enzymes [1]. The COX pathways generate prostaglandins (PGs) and thromboxanes (TXs); the LOX pathways produce leukotrienes (LTs) and lipoxins (LXs); and the cytP450 pathways produce a range of hydroxy-, epoxy- and dihydroxy-derivatives [1]. Many of these are biologically active. However, because they are rapidly catabolised, eicosanoids mainly act locally to the site of their production. Because of its content in cell membrane phospholipids, the omega-6 (*n*-6) PUFA arachidonic acid (ARA; 20:4*n*-6) is the most common substrate for eicosanoid synthesis. Alternative substrates include another *n*-6 PUFA, dihomo-γ-linolenic acid (20:3*n*-6) and the *n*-3 PUFA eicosapentaenoic acid (EPA: 20:5*n*-3). The functional activities of eicosanoids produced from ARA are better described than those produced from other substrate PUFAs. Eicosanoids have roles in inflammation and immune regulation and in the vascular, renal, gastrointestinal and reproductive systems as well as elsewhere. As such, they are important physiologically, but they are also linked to system dysfunction and disease. Therefore, there has been significant interest in development of inhibitors of eicosanoid synthesis and activity for disease prevention and treatment. This article will describe the pathways of eicosanoid synthesis; eicosanoid receptors; the action of eicosanoids in different physiological systems; the roles of eicosanoids in selected diseases; and the major inhibitors of eicosanoid synthesis and action. Table 1 shows the structures of selected eicosanoids.

## Eicosanoid biosynthesis from arachidonic acid

The enzymes initiating eicosanoid biosynthesis utilise unesterified PUFAs as substrates. Normally the unesterified concentrations of PUFAs within cells are low, meaning that they must be released from cell membrane phospholipids prior to entering the COX, LOX or cytP450 pathways. Phospholipase enzymes, particularly the phospholipase A2 ($PLA_2$) family, are responsible for release of PUFAs from phospholipids, mainly from the *sn*-2 position (Figure 1). There are a number of members of the $PLA_2$ family [2], but $Ca^{2+}$-dependent cytosolic $PLA_2$ ($cPLA_2$) seems to be very important for eicosanoid biosynthesis because of its substrate specificity [3]: cPLA2 is able to release PUFAs from the *sn*-2 position of phosphatidylcholine, the major phospholipid in most mammalian cell membranes, and phosphatidylinositol (Figure

1). There are also $Ca^{2+}$-independent cytosolic $PLA_2$ and secretory $PLA_2$ enzymes [2]. The activity of $PLA_2$ enzymes is increased in response to various stimuli such as adrenaline [2]. As the name suggests, the $Ca^{2+}$-dependent $cPLA_2$ responds to increases in cytosolic $Ca^{2+}$ concentrations, which promote the enzyme's movement from the cytosol to cell membranes (particularly the endoplasmic reticulum and the nuclear membrane) where it comes into contact with the substrate phospholipids. The enzyme is activated by phosphorylation by mitogen-activated protein kinases. When phosphorylation is coupled with an increase in cytosolic $Ca^{2+}$, cPLA2 becomes active [2,3]. An alternative source of 20-carbon PUFAs is hydrolysis from the *sn*-2 position of diacylglycerol by diacylglycerol lipase, with the diacylglycerol having been generated by phospholipase C-mediated hydrolysis of phosphatidylinositol 4,5-bisphosphate (Figure 1).

Once released, the 20-carbon PUFA can enter the COX [4], LOX [5,6] or cytP450 [7-10] pathways. The COX pathway produces PGs and TXs, which are collectively termed prostanoids (Figure 2). The first steps of the COX pathway are two sequential reactions both catalysed by PG endoperoxide H synthase: a COX reaction that produces $PGG_2$ from ARA and a peroxidation reaction that then produces $PGH_2$; PG endoperoxide H synthase is loosely termed COX. There are two main isoforms of COX, COX-1 and COX-2 [11,12]; there is also a variant of COX-1 termed COX-3 that seems not to be functional in humans [13]. COX-1 is constitutively expressed and is considered to produce PGs required for basal physiological function [11,12]. COX-2 is inducible, for example by bacterial products such as lipopolysaccharide and by some inflammatory cytokines [11,12]. The two different reactions catalysed by COX enzymes take place at two different sites of the enzyme, but they are coupled together. The active sites of COX-1 and COX-2 are similar, but the COX-2 active site is larger, a feature that has been exploited in development of drugs to target ARA metabolism. ARA is the preferred substrate for both COX-1 and COX-2 [14].

$PGH_2$ is unstable and its metabolism by a series of prostanoid synthases yields $PGD_2$, $PGE_2$, $PGF_{2\alpha}$, $PGI_2$ (also called prostacyclin) and $TXA_2$ (Figure 2). Most of the prostanoid synthases have multiple subtypes with different tissue distributions [15]. What this means is that different cell types have different capabilities to produce these eicosanoids. For example, $TXA_2$ is produced by activated platelets [16-18] while $PGI_2$ is produced by vascular endothelial cells [19-21]. The prostanoid synthases are often coupled to the different COX enzymes: cytosolic PGE synthase and TXA synthase are coupled to COX-1 while membrane PGE synthase and

PGI synthase are coupled with COX-2. $PGD_2$, $PDE_2$, $PGI_2$ and $TXA_2$ can be further metabolised. Of note, $PGD_2$ is converted to 15-deoxy-$PGJ_2$ via $PGJ_2$ (Figure 2).

There are several LOX enzymes [5,6,22]. 5-LOX is involved in formation of LTs (Figure 3). In humans, 5-LOX is expressed mainly in cells of myeloid origin (neutrophils, eosinophils, monocytes, macrophages, mast cells and dendritic cells) [5,6]. In resting cells, 5-LOX is found in the cytosol or in the nucleus as a soluble enzyme, depending on the cell type. In response to cell activation, 5-LOX co-migrates with $PLA_2$ to the endoplasmic reticulum and nuclear membrane. In the first step of the 5-LOX pathway 5-hydroperoxyeicosatetraenoic acid (5-HpETE) is produced from ARA. 5-HpETE can be reduced to 5-hydroxyeicosatetraenoic acid (5-HETE) or can be further metabolised by 5-LOX. This step requires 5-LOX activating protein (FLAP) and coactosin-like protein and yields 5,6-epoxyeicosatetraenoic acid, also known as $LTA_4$. $LTA_4$ is unstable but is metabolised further along two routes (Figure 3). One of these uses the cytosolic enzyme $LTA_4$ hydrolase (sometimes called $LTB_4$ synthase) to form $LTB_4$ [23]. The other uses the nuclear membrane bound glutathione-S-transferase to insert the tripeptide glutathione onto $LTA_4$ to form $LTC_4$ which is further metabolised to $LTD_4$ and on to $LTE_4$. $LTC_4$, $D_4$ and $E_4$ are together termed peptido-LTs or cysteinyl-LTs and are sometimes collectively referred to as “slow reacting substance [of anaphylaxis]”.

15-LOX (15-LOX type 2) generates 15-HpETE from ARA. This can be reduced to 15-HETE and then converted by 5-LOX to a 5,6-epoxyeicosatetraenoic acid. This metabolite is the precursor to both $LXA_4$ and $LXB_4$ [24]. Epimers of $LXA_4$ and $LXB_4$ can also be produced from ARA as a result of COX-2 activity in the presence of aspirin; hence these epimers are sometimes referred to as aspirin-triggered LXs [24]. Another mechanism links the LT and LX pathways: $LTA_4$, synthesised by the 5-LOX pathway in leukocytes as described earlier, can be released and is taken up by platelets where 12-LOX forms $LXA_4$ (Figure 4) [25]. The 12/15-LOX (15-LOX type 1) in eosinophils and mast cells produces LT analogues called eoxins from ARA [26]. 12-LOX produces hepoxilans, mainly in the epidermis [27].

CytP450 enzymes are membrane bound monooxygenases; they require NADPH for activity. There are a number of cytP450 enzymes capable of metabolising ARA according to two distinct pathways (Figure 5). Omega-hydroxylases, such as cytP450 4A and 4F convert ARA to different HETEs (e.g. 12-, 15-, 16-, 17-, 18-, 19- or 20-HETE). CytP450 epoxygenases, such as cytP450 2C8, 2C9, 2C19 and 2J2, convert ARA to one of several epoxyeicosatrienoic acids (EETs: 14,15-, 11,12-, 8,9- or 5,6-EET) [7-10]. EETs are produced by many different cell

types, including leukocytes, endothelial cells, astrocytes and cardiac myocytes. EETs are rapidly metabolised in pathways involving epoxide hydrolases to form dihydroxyeicosatrienoic acids. In general, the dihydroxyeicosatrienoic acids are less active than the EETs. The balance of cytP450 metabolites produced depends upon the cell type and specific cytP450 isoform involved.

**Eicosanoid receptors**

Most eicosanoids mediate their effects via G-protein coupled receptors [28]. Table 2 lists the ligands and signalling pathways for each of the receptors for metabolites of the COX and LOX pathways. Eicosanoids can have many target cells, tissues and biological processes and therefore have multiple key roles in physiology. The eicosanoid G-protein coupled receptors signal through stimulation or inhibition of generation of second messengers such as cyclic adenosine monophosphate (cAMP) and $Ca^{2+}$. The prostanoid receptors are designated $DP_1$ and $DP_2$ for PGD; $EP_1$, $EP_2$, $EP_3$, $EP_4$ for PGE; FP for PGF; TP for TXs; and IP for PGI [29]. Although each prostanoid binds with the highest affinity to its cognate receptor, there is considerable cross-reactivity between the prostanoids and the prostanoid receptors (Table 2). For example, the $DP_1$ and $DP_2$ receptors bind $PGD_2$, $PGE_2$ and $PGF_{2\alpha}$ although the affinity is greatest for $PGD_2$. These same prostanoids can all bind to the FP receptor, but this has greatest affinity for $PGF_{2\alpha}$. The IP receptor is the least selective prostanoid receptor. 15-deoxy-$PGJ_2$ has no cell surface receptor but instead binds the nuclear peroxisome proliferator-activated receptor (PPAR)-γ [30], which is a key regulator of adipogenesis, insulin sensitivity and inflammation. In addition to its G-protein coupled receptor IP, $PGI_2$ binds PPARδ [31].

The LTB receptors are $BLT_1$ and $BLT_2$, while the cysteinyl-LT receptors are $CysLT_1$, $CysLT_2$ and $CysLT_3$ (also known as GPR99) [28] (Table 2). $BLT_1$ displays high affinity for LTB while $BLT_2$ has lower affinity. $CysLT_1$ has highest affinity for LTD followed by LTC and then LTE, while $CysLT_2$ has highest affinity for LTC and LTD with lower affinity for LTE. $CysLT_3$ has highest affinity for LTE. Cysteinyl-LTs can also bind to GPR17, while LTE can bind to the purinergic receptor P2Y12 [28]. Some LTs, including $LTB_4$, can bind PPARs [32]. The receptor for LXA is ALX, also known as formyl peptide receptor 2 [33]. $LXA_4$ antagonises the $CystLT_1$ receptor [28]. $LXA_4$ is a ligand for the nuclear aryl hydrocarbon receptor [34].

EETs bind PPARα and PPARγ [35] and may also have G-protein coupled receptors [36,37].

**Eicosanoids, inflammation and immunity**

The role of eicosanoids in inflammation and immunity is, perhaps, the most widely explored of their biological activities [38-45]. Inflammation is a part of normal host defence, playing important early roles in immunity against infections and in wound healing. Infection and inflammatory stimuli activate $PLA_2$, COX-2 and 5-LOX increasing the capacity for eicosanoid generation. Some eicosanoids are known to mediate the cardinal signs of inflammation: redness, pain, fever and swelling. However, it is important to note that, while many of the activities of eicosanoids may be described as pro-inflammatory, they also have anti-inflammatory roles and some are even involved in resolution of inflammation. These various activities are related to the precise signalling processes induced by the different eicosanoid receptors and the timing of eicosanoid production. The nature of the inflammatory stimulus and the types of cells present determine the mix of eicosanoids produced at any given time during the inflammatory response. For example, mast cells produce high amounts of $PGD_2$, while monocytes and macrophages produce high amounts of $PGE_2$.

The pleiotropic effects of eicosanoids within inflammation are well illustrated by $PGE_2$, which has many pro-inflammatory roles such as inducing fever and pain and enhancing vascular permeability, which allows neutrophils, mast cells and macrophages to enter sites of infection or inflammation [38,39]. $PGE_2$ also potentiates the pain response induced by other mediators like bradykinin and histamine. Because of these actions, many anti-inflammatory pharmaceuticals target the COX pathway with the aim of decreasing $PGE_2$ production. However, $PGE_2$ is able to suppress the production of classic pro-inflammatory cytokines like tumour necrosis factor, interleukin-1β and interleukin-6 [46]. $PGE_2$ also suppresses 5-LOX, inhibiting synthesis of LTs (which are generally pro-inflammatory) and induces 15-LOX to promote the synthesis of pro-resolution LXs [47,48] (Figure 6). Hence, the actions of this one eicosanoid in inflammation are complex: it possesses both pro- and anti-inflammatory actions and is involved in the induction of inflammation resolution. Therefore, $PGE_2$ should be regarded as both a mediator and a regulator of inflammation with roles in its initiation, propagation and resolution. Inflammation is an early response to infection or tissue injury, while acquired immunity, which involves antigen presenting cells (dendritic cells are professional antigen-presenting cells), T-lymphocytes (T-cells) and B-lymphocytes (B-cells), is slower to develop. $PGE_2$ has effects on acquired immunity [38-41]. It decreases many of the

functions of dendritic cells including their interactions with T-helper 1 (Th1) lymphocytes, cytotoxic T-lymphocytes and natural killer cells. With regard to effects on T-lymphocytes, $PGE_2$ is generally regarded as immunosuppressive, since it decreases T-cell proliferation, the production of key cytokines like interlukin-2 and interferon-γ, the differentiation of naïve T-cells to Th1 cells and cytotoxic T-cells, and the killing functions of cytotoxic T-cells and natural killer cells. These effects are mediated in part by induction of regulatory T-cells which act to suppress Th1 and cytotoxic T-cell activity. Since dendritic cells, Th1 cells, cytotoxic T-cells and natural killer cells are central to host defence against pathogenic organisms (especially bacteria and viruses) and cancer cells, these effects may be considered to be deleterious. The Th1 cell response is balanced with the T-helper 2 (Th2) type response that involves interleukins 4, 5 and 13 and is part of defence against extracellular parasites like helminthic worms. $PGE_2$ promotes the Th2 type immune response [39-41]. Thus, with regard to T-cell-mediated immunity, $PGE_2$ should be viewed as an important regulator, perhaps playing a role in assuring that the most appropriate response to a particular pathogen is generated. The balance of Th1 and Th2 cells affects B lymphocyte function and antibody production. Both through its effects on Th2 cells and through direct effects on B-cells, $PGE_2$ promotes immunoglobulin class switching to favour production of immunoglobulin E which is involved in allergic responses. $PGE_2$ induces differentiation of pro-inflammatory T-helper 17 cells [49].

$PGD_2$ is released from mast cells as an allergic and inflammatory mediator [39,42]. It has a significant proinflammatory effect especially in allergic airways disease (asthma), where it up-regulates some of the hallmark characteristics including eosinophilia, airway hyperreactivity, mucus production, and Th2 cytokine production [50]. $PGD_2$ also has pro-inflammatory effects in the skin where it promotes erythema, oedema, induration, and leukocyte infiltration [51]. As a vasodilator, $PGD_2$ contributes to inflammation by increasing local blood flow. Despite these well described pro-inflammatory and pro-allergic actions, $PGD_2$ has also been described in animal models to have some anti-inflammatory and inflammation resolving effects, again revealing pleiotropic characteristics. $PGD_2$ also has effects within acquired immunity but these are not well described, although, like $PGE_2$, it has been reported to suppress the Th1-medated response [41].

LOX products are also important in inflammation and immunity [5,6,39,43,44,52]. $LTB_4$ is produced by many different types of leukocyte particularly neutrophils and macrophages and also by epithelial cells. It is a bronchoconstrictor, increases vascular permeability and is a potent chemoattractant, acting to recruit leukocytes (especially neutrophils and macrophages)

to sites of inflammatory or immune activity [5,6,39,53]. $LTB_4$ also enhances leukocyte adhesion to the endothelium. It induces production of reactive oxygen species and proteolytic enzymes by various target cells, particularly neutrophils, and production of pro-inflammatory cytokines like tumour necrosis factor, interleukin-1β, interleukin-6 and interleukin-8 by neutrophils and macrophages. Thus, the effects of $LTB_4$ are pro-inflammatory. $LTB_4$ is also known to influence the function of T-lymphocytes (increased proliferation and interleukin-2 and interferon-γ production, suggesting enhanced Th1 cell function), B-lymphocytes (differentiation and increased immunoglobulin E production) and natural killer cells (enhanced cytotoxicity) [53]. Hence $LTB_4$ seems to promote immune defences.

The cysteinyl-LTs ($LTC_4$, $D_4$ and $E_4$) are produced primarily by basophils, eosinophils, mast cells and macrophages following exposure to various stimuli, for example allergens. They enhance vascular permeability, promote eosinophil recruitment to the airways and are potent inducers of smooth muscle contraction, including in the airways (bronchoconstriction) where they have a role in asthma [5,6,39,44,54]. They also induce mucus production by goblet cells and oedema and activate various pro-inflammatory responses of mast cells, macrophages and neutrophils, such as generation of reactive oxygen species, cytokines and proteases. Cysteinyl-LTs promote the Th2 response, with $LTE_4$ being the most active.

Different HETEs and EETs are involved in inflammation with varying actions. For example, 20-HETE is generally regarded as pro-inflammatory [55,56], acting to increase reactive oxygen species generation, expression of cellular adhesion molecules and pro-inflammatory cytokine production. In contrast, effects of EETs are generally anti-inflammatory [57], acting to inhibit inflammatory cytokine production and leukocyte-endothelial adhesion.

Resolution is important to end the inflammatory response in an ordered and integrated manner. It is now considered that loss of resolution results in ongoing inflammation that can become damaging and induce pathological changes. The resolution of inflammation occurs because various inhibitory mechanisms are activated as inflammation runs its course [58]. A central mechanism involved is the generation of specialised pro-resolving lipid mediators which act to inhibit pro-inflammatory signalling [59-61]. Amongst the most important of these are the LXs and their 15-epimers, the AT-LXs, derived from ARA metabolism (see earlier) [24]. These are formed by several alternative pathways involving 5-, 12- and 15-LOX and aspirin-acetylated COX-2 by leukocytes, platelets, the vascular endothelium and the epithelium, alone or via transcellular interactions (e.g. Figure 6). LXs and AT-LXs exert potent effects on leukocytes,

vascular and epithelial cells to stop inflammation and promote resolution [62,63]. They have been shown to be beneficial in a broad range of preclinical models of disease [62,63]. It is also claimed that some EETs are involved in resolution of inflammation [64,65].

**Eicosanoids and the vascular system**

Eicosanoids are involved in platelet aggregation, haemostasis, thrombosis and regulation of vascular tone [16-21,66]. Many eicosanoids act as vasodilators (e.g. $PGI_2$, $PGE_2$, some EETs) or vasoconstrictors (e.g. $TXA_2$, cysteinyl-LTs, 20-HETE, some EETs), therefore affecting blood flow and blood pressure. A pair of prostanoids, $TXA_2$ and $PGI_2$, play a central role in vascular homeostasis and control of blood flow through their actions on platelets and on vascular smooth muscle cells. $TXA_2$ is mainly produced by platelets (via COX-1) and its production is increased when platelets are activated. It promotes smooth muscle contraction, acting as a vasoconstrictor, and is a potent activator of platelets causing their aggregation leading to thrombus formation. $PGI_2$ is mainly produced by endothelial cells. It is a potent vasodilator and inhibits platelet aggregation and smooth muscle cell proliferation. Hence, the balance in production of $TXA_2$ and $PGI_2$ establishes vascular tone and thrombotic potential. $PGD_2$ is an inhibitor of platelet aggregation [67]. $PGE_2$ also affects platelets but has more complex effects related to its concentration [67]. At low concentrations it acts synergistically with $TXA_2$ to promote platelet aggregation and oppose the effects of $PGI_2$. However, at high concentrations $PGE_2$ can act through the IP receptor and perhaps through the DP receptors to inhibit platelet aggregation. 12- and 15-HETE are other prostanoid modulators of platelet activity.

There is an interesting interaction between eicosanoids and the nitric oxide (NO) system that is relevant to the vascular system [68] (Figure 7). NO increases COX activity in endothelial cells, due to the formation of peroxynitrite from the interaction of NO and superoxide anions; peroxynitrite directly activates COX. However, although $PGI_2$ is usually the principal prostanoid produced by this system, peroxynitrite inhibits PGI synthase. Consequently, $PGH_2$ accumulates and is believed to act via the TP receptor to promote smooth muscle contraction and cause vasoconstriction. Conversely some prostanoids, including $PGI_2$, induce the endothelial nitric oxide synthase that produces NO. These findings suggest a complex interaction between superoxide, NO and COX-generated prostanoids in the control of vascular tone.

## Eicosanoids and the renal system

Prostanoids in the kidney are generated by both COX-1 and COX-2 and have roles in regulating renal blood flow and glomerular filtration rate [69,70]. The COX and PG synthase enzymes have different distributions within the kidney, as do the prostanoid receptors [69]. $PGE_2$ is the most abundant eicosanoid synthesized in the kidney. COX-1 is involved in haemodynamic regulation, with $PGE_2$ principally involved. COX-2 expression is regulated in response to intravascular volume and is important in maintaining salt and water homeostasis, again largely involving $PGE_2$ [69,70]. $PGE_2$ interacts with the renin-angiotensin system to regulate blood pressure [70]. A high-salt diet increases renal medullary COX-2 expression resulting in $PGE_2$ production [70]. The resulting change in salt and water reabsorption serves to control renal medullary blood flow and blood pressure. $PGI_2$ increases potassium secretion and because of its vasodilatory properties it increases renal blood flow and glomerular filtration rate [70,71]. LOX metabolites including 12- and 15-HETE and cytP450 metabolites including 20-HETE and several EETs also have roles in renal function [70,72].

## Eicosanoids and the gastrointestinal system

COX-1 is constitutively expressed throughout the gastrointestinal tract and prostanoids derived from COX-1, especially $PGI_2$ and $PGE_2$, have important cytoprotective effects on the gastrointestinal mucosa maintaining its integrity [73]. Both $PGI_2$ and $PGE_2$ reduce acid secretion by gastric parietal cells, increase mucosal blood flow and stimulate the release of mucus. COX-2 is induced if there is gastrointestinal damage (e.g. ulceration) and the PGs produced play a role in healing [73].

## Eicosanoids and the female reproductive system

Prostanoids are involved in many reproductive processes from ovulation and fertilisation to induction of labour and parturition [74-76]. $PGE_2$ has a prominent role in female fertility, including actions related to ovulation, fertilization, embryo development and early implantation [74]. ARA release is tightly regulated by follicle-stimulating and luteinizing hormones during oocyte development. $PGE_2$ has multiple roles in the ovulatory cascade, including induction of several ovulatory genes and promotion oocyte meiotic maturation,

cumulus expansion and follicle rupture. It also reduces extracellular matrix viscosity, thereby optimising the conditions for sperm penetration. $PGE_2$ decreases the phagocytic activity of neutrophils against sperm in the oviduct so ensuring sperm survival. $PGE_2$ also acts on sperm to enhance its function and binding capacity to oocytes. $PGE_2$ maintains luteal function for embryo development and early implantation: $PGE_2$ secreted by the embryo, ovary, corpus luteum, oviduct and endometrium stimulates cleavage, survival, and blastocyst formation and hatching rates in the intrauterine cavity. In addition, $PGE_2$ induces chemokine expression for trophoblast apposition and adhesion to the decidua for embryo implantation. There is evidence that $PGE_2$ promotes embryo growth, proliferation, differentiation and survival. Thus, $PGE_2$ plays important roles in oocyte maturation, in fertilisation and in establishing the early embryo [74].

There is also evidence for the involvement of prostanoids once pregnancy is established [75]. Secretory PLA2, cPLA2, COX-1, COX-2 and prostanoid receptors are all expressed in the uterus during pregnancy [75]. Prostanoids are produced in the fetus, the placenta and the uterine tissues and are considered to have a central role in the maintenance of pregnancy. $PGE_2$, $PGF_{2\alpha}$, $TXA_2$ and $PGI_2$ have all been described to be present in the myometrium during pregnancy [75]. $PGI_2$ is important in maintaining uterine smooth muscle relaxation during pregnancy, but this effect must be overcome in anticipation of birth. $PGE_2$, $PGF_{2\alpha}$ and $TXA_2$ all contract uterine smooth muscle.

Prostanoids have a central role in the initiation of labour, with the change from uterine quiescence to a contractile state associated with differential expression of prostanoid receptors within the myometrium and fetal membranes (i.e. the amnion and chorion leave) which form the amniotic sac and the attached decidua [76]. In advance of labour secretory $PLA_2$, $cPLA_2$ and COX-2 expression are increased (mainly in fetal membranes), as are the amniotic fluid and blood concentrations of $PGE_2$ and $PGF_{2\alpha}$. Progesterone, oestrogen and glucocorticoids may be important regulators of these labour-related changes in ARA metabolism. PGs ripen the cervix, change membrane structure and contract the myometrium [76]. $PGE_2$ is 8 to 10-times more potent than $PGF_{2\alpha}$ in stimulating human myometrial contractions [76]. Interestingly, the pattern of uterine contractions from the fundal region of the uterus towards the cervix with a loss of intensity parallels the distribution of the various EP receptors. $PGE_2$ and $PGF_{2\alpha}$ have been used to induce labour while inhibition of PG production delays labour [76].

**Eicosanoids in disease**

Eicosanoids have many roles in physiology (as outlined above) and the normal functioning and regulation of many physiological systems, such as inflammation, thrombosis and vascular tone, clearly involves balancing the opposing activities of different members of the eicosanoid family. Inappropriate, excessive or imbalanced production of one or more of the eicosanoids involved could result in failure of the normal regulatory processes leading to loss of homeostasis and in some cases disease. Examples where this occurs include inflammatory disease and cancer.

Chronic inflammatory diseases include rheumatoid arthritis, inflammatory bowel disease and asthma. Rheumatoid arthritis is a destructive disease of the joints, which show infiltration of activated T-lymphocytes (mainly Th1 cells), macrophages and antibody-secreting B-lymphocytes into the synovium (the tissue lining the joints) and proliferation of fibroblast-like synovial cells called synoviocytes. These cells and new blood vessels form a tissue termed pannus which leads to progressive destruction of cartilage and bone. Eicosanoids are central to the pathology of rheumatoid arthritis: expression of both COX-1 and COX-2 is increased in the synovium of patients [77] and the synovial fluid contains high levels of eicosanoid products of both the COX and LOX pathways [77,78]. Infiltrating leucocytes such as neutrophils, and monocytes and synoviocytes are important sources of eicosanoids in RA, which contribute to the ongoing inflammatory state that is linked to tissue destruction.

Inflammatory bowel disease affects the gastrointestinal mucosa. The two main forms of inflammatory bowel disease are Crohn's disease, which can affect any part of the gastrointestinal tract, and ulcerative colitis, which primarily affects the colon. In both forms of inflammatory bowel disease there are large infiltrates of neutrophils into the inflamed tissue, although other inflammatory cell types are also present. There are different T-cell response profiles associated with ulcerative colitis (Th2 predominant) and Crohn's disease (Th1 predominant). Eicosanoids are also involved in inflammatory bowel disease: the intestinal mucosa contains elevated levels of inflammatory eicosanoids derived from ARA including $PGD_2$, $PGE_2$, $TXA_2$, $LTB_4$ and several HETEs [79,80] and these are related to disease activity or severity [80].

Asthma affects the airways. It is characterized by reversible airflow obstruction and bronchospasm, due to increased contractility of the surrounding smooth muscles, and common symptoms include wheezing, coughing, chest tightness, and shortness of breath. Asthma is

characterised by leukocytic infiltration into the lungs; there is a predominance of eosinophils but other cell types including mast cells, neutrophils, macrophages and T lymphocytes (Th2 predominant) are present. There is increased production of ARA-derived eicosanoids, including $PGD_2$ and the cysteinyl-LTs [53,54,81-83] (Figure 8). The LTs are detected in the blood, bronchoalveolar lavage fluid and urine. In addition to the role of ARA-derived eicosanoids as mediators of the symptoms of asthma, like bronchoconstriction, $PGE_2$ is also involved in regulating the development of the Th2 phenotype of T lymphocytes that predispose to allergic inflammation and promotes the formation of immunoglobulin E by B lymphocytes [39-41,81] (Figure 8).

There are many reports of increased or over-expression of COX-2 in a variety of cancers including breast, colon and prostate [84]. Several prostanoids have roles in supporting tumour cell proliferation, survival, migration and invasion [85]. $PGE_2$ seems to be especially important in this regard, and often occurs at much higher concentrations in tumour than in normal tissues, although other eicosanoids, including $LTB_4$ share some of the same roles [85]. The effects of $PGE_2$ on acquired immunity may also contribute to a permissive role in tumour development. Reports of the effects of $PGD_2$ on tumour promotion are conflicting [86]. $TXA_4$ has pro-cancer activities rather like those of $PGE_2$ [87], and as is often the case, these activities are balanced by that of $PGI_2$ [88]. In contrast to the effects of $PGE_2$, $TXA_2$ and $LTB_4$, 15 deoxy-$PGJ_2$ acts via PPAR-γ to inhibit tumour cell proliferation and stimulate apoptosis [89]. 15 deoxy-$PGJ_2$ also inhibits tumour cell migration and angiogenesis [89].

**Inhibitors of eicosanoid synthesis and action**

The discovery that aspirin inhibits COX activity and prostanoid production [90] and the recognition that eicosanoids are mediators of processes linked to pathology and disease, such as inflammation and thrombosis, opened up eicosanoid synthesis and action as potential targets for pharmaceutical intervention (Figure 9). Aspirin is termed a non-steroidal anti-inflammatory drug (NSAID). Aspirin acts by acetylation of the active site of both COX-1 and COX-2. This causes irreversible inhibition of COX-1 but changes the function of COX-2 so that PGs are not formed. Rather, in the presence of aspirin, COX-2 catalyses a LOX-like reaction. Other NSAIDs include ibuprofen, indomethacin and diclofenac and these reversibly inhibit both COX-1 and COX-2. Because NSAIDs inhibit the production of prostanoids they are anti-inflammatory, antipyretic and analgesic. However, they inhibit prostanoid production by both

COX-1 and COX-2 and so are not selective. Because of the resulting inhibition of COX-1-mediated homeostatic functions, NSAIDs can have unwanted side effects such as gastric ulceration, bleeding and renal dysfunction. Selective COX-2 inhibitors (e.g. celecoxib) are anti-inflammatory and analgesic with generally good gastrointestinal safety [91-93]. However, these drugs have prothrombotic properties. COX-2 inhibitors suppress production of $PGI_2$ by the endothelium but do not suppress $TXA_2$ production by platelets which is largely due to COX-1 activity. Hence, COX-2 inhibitors favour platelet aggregation, thrombosis and vasoconstriction, so increasing cardiovascular risk [94]. Aspirin does not have this effect because it inhibits $TXA_2$ production by COX-1 and has limited effect on $PGI_2$ production, hence creating an anti-thrombotic and vasodilatory environment.

There are putative inhibitors to most of the enzymes involved in eicosanoid synthesis and antagonists to several eicosanoid receptors. Not all of these have reached the clinic but those that have are mainly used to treat inflammation, but they clearly have applications in any area where aberrant eicosanoid production or action has a pathological consequence. Glucocorticoids are endogenous or synthetic anti-inflammatory steroid hormones that act to increase the synthesis and function of annexin A1 (also known as lipocortin-1) [95]. Annexin A1 inhibits $PLA_2$ activity, so reducing availability of ARA as a substrate for eicosanoid synthesis [95]. Glucocorticoids also reduce expression of COX-1 and COX-2 protein [96].

There are inhibitors of 5-LOX (e.g. zileuton), FLAP, $LTA_4$ hydrolase and $LTC_4$ synthase and antagonists of BLT and CysLT receptors (e.g. montelukast) that are being trialled or are already in use to treat asthma [97].

Inhibitors of soluble epoxide hydrolase that degrades EETs are being developed for a multitude of uses including in inflammatory, vascular and renal diseases [98,99].

**EPA as an alternative eicosanoid substrate**

COX, LOX and cytP450 enzymes are active towards a number of 20-carbon PUFAs other than ARA, generating alternative families of eicosanoids (they are also active towards some 18- and 22-carbon PUFAs). Eicosanoids produced from the *n*-3 PUFA EPA have received attention because they often have different potencies to those produced from ARA. The generation of eicosanoids from EPA uses the same enzymes as the pathway of generation from ARA. However, because the structure of the substrate PUFAs differs, the structure of eicosanoids

produced differs: whereas 2-series prostanoids and 4-series LTs are produced from ARA, EPA gives rise to 3-series prostanoids and 5-series LTs. The omega hydroxylases produce hydroxyeicosapentaenoic acids from EPA, while the cytP450 epoxygenases produce epoxyeicosatetraenoic acids. The phospholipids of blood cells involved in inflammatory processes taken from humans consuming a typical Western diet typically contain 15 to 20% of fatty acids as ARA and 0.5 to 1% as EPA [100,101]. COX and LOX enzymes prefer ARA over EPA as a substrate. For example, ARA was more than 10-times more effective than EPA as a substrate for COX-1 and 3.3-times more effective as a substrate for COX-2 [102]. Therefore, because the content of EPA in cell membrane phospholipids is much lower than the ARA content and because ARA is preferred by COX and LOX enzymes, EPA is usually only a minor contributor to eicosanoid generation. However, increased intake of EPA, or of its precursors, increases its membrane content [100,101]. This provides an increased amount of substrate for eicosanoid synthesis. Furthermore, increased incorporation of EPA is at the expense of ARA [100,101], decreasing ARA availability. Hence, EPA results in decreased production of ARA-derived PGs, TXs and LTs by inflammatory cells [103-106] and platelets [107-109] and in increased production of the EPA-derived analogs. In general, the structural difference between ARA and EPA-derived eicosanoids renders the latter less biologically effective. This has been clearly demonstrated for the action of $LTB_5$ versus $LTB_4$ as a leukocyte chemoattractant where the former is 10 to 100-fold less potent [109,110]. One reason for this reduced biological potency is that the EPA-derived mediators are less effective ligands for eicosanoid receptors than the ARA-derived eicosanoids. This was explored in detail for prostanoid receptors by Wada et al. [102] who identified, for example, 50 to 80% lower effectiveness of $PGE_3$ compared with $PGE_2$ towards the $EP_1$, $EP_2$, $EP_3$ and $EP_4$ receptors. Likewise, $PGF_{3\alpha}$ was 80% less effective than $PGF_{2\alpha}$ towards the FP receptor. Thus, EPA results in decreased production of potent eicosanoids from ARA and in increased production of generally weaker eicosanoids; this may be one mechanism to explain the reported anti-inflammatory effects of EPA [111-113]. However, there are some exceptions to this: $PGI_3$ was only 20% less effective towards the IP receptor than $PGI_2$ [102]. This may relate to the inhibitory effect of EPA on platelet aggregation [106-108]. High intakes of EPA result in decreased production of both $TXA_2$ and $PGI_2$ and increased production of $TXA_3$ and $PGI_3$ [106-108]. $TXA_3$ is a weak platelet aggregator but $PGI_3$ has similar anti-aggregatory potency to $PGI_2$ [114,115]. Therefore, high intakes of EPA create an anti-aggregatory environment. This has been suggested as one mechanism by which *n*-3 PUFAs reduce cardiovascular mortality [116]. Wada et al. [102]

demonstrated that $PGD_3$ is a more effective ligand for the $DP_1$ receptor than is $PGD_2$, although the $DP_2$ receptor does not discriminate between the two PGDs. The epoxyeicosatetraenoic acids may have more potent vascular effects than the EETs [117,118].

Using the COX and LOX enzymatic machinery, EPA (and its longer chain, more unsaturated derivative docosahexaenoic acid) gives rise to mediators that are very active in the resolution of inflammation, termed specialised pro-resolution mediators (resolvins, protectins and maresins). The biosynthesis, structures and actions of these mediators are described in detail elsewhere [53-55,119].

## Summary

- Eicosanoids are oxidised derivatives of 20-carbon polyunsaturated fatty acids formed by the cyclooxygenase, lipoxygenase and cytochrome P450 pathways; arachidonic acid is the usual substrate
- Eicosanoids are highly bioactive acting on many cell types through cell membrane G-protein coupled receptors, although some eicosanoids are also ligands for nuclear receptors
- Many eicosanoids have multiple, sometimes pleiotropic, effects on inflammation and immunity
- Many eicosanoids have roles in the regulation of the vascular, renal, gastrointestinal and female reproductive systems
- Despite their vital role in physiology, eicosanoids are often associated with disease, including inflammatory disease and cancer
- Inhibitors have been developed that interfere with the synthesis or action of various eicosanoids and some of these are used in disease treatment, especially for inflammation

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**Figure captions**

Figure 1. Phospholipase-mediated hydrolysis of phospholipid substrates to release the *sn*-2 fatty acid. A) Phospholipase $A_2$ ($PLA_2$) removes the fatty acid from the *sn*-2 position of phospholipid substrates, particularly phosphatidylcholine, to yield a 1-acyl lysophospholipid. B) Phospholipase C (PLC) removes the polar head group from phospholipid substrates, particularly phosphatidylinositol 4,5-bsphosphate, to yield a 1,2-diacylglycerol and the free head group (e.g. inositol 1,4,5-trisphosphate). Subsequently, diacylglycerol lipase (DAG lipase) removes the fatty acid from the sn-2 position of the diacylglycerol to yield a 1-monoacylglycerol. $R_1$ and $R_2$ represent two different fatty acid chains. For eicosanoid biosynthesis $R_2$ would be a 20-carbon polyunsaturated fatty acid, most commonly arachidonic acid.

Figure 2. Outline of the pathway of biosynthesis of prostaglandins and thromboxanes from arachidonic acid. PG, prostaglandin; PGDS; prostaglandin D synthase; PGES; prostaglandin E synthase; PGH 9,11-ER, prostaglandin H 9,11-endoperoxide reductase; PGIS; prostaglandin I synthase; TX, thromboxane; TXAS, thromboxane A synthase.

Figure 3. Outline of the pathway of biosynthesis of leukotrienes from arachidonic acid. HETE, hydroxyeicosatetraenoic acid; HpETE, hydroperoxyeicosatetraenoic acid; FLAP, 5-lipoxygenase activating protein; LT, leukotriene.

Figure 4. Transcellular synthesis of lipoxin $A_4$. Leukotriene (LT)$A_4$ is released from leukocytes and taken up by platelets where it acts as a substrate for 12-lipoxygenase, ultimately producing lipoxin (LX)$A_4$.

Figure 5. Outline of the pathway of cytochrome P450 mediated metabolism of arachidonic acid. DHET, dihydroxyeicosatrienoic acid; EET, epoxyeicosatrienoic acid; HETE, hydroxyeicosatetraenoic acid.

Figure 6. Depiction of the role of prostaglandin $E_2$ in regulating the biosynthesis of 4-series leukotrienes and lipoxin $A_4$. Prostaglandin (PG)$E_2$ is produced by the cyclooxygenase (COX) pathway and 4-series leukotrienes (LTs) are produced by the 5-lipoxygenase (5-LOX) pathway. During the course of the inflammatory response $PGE_2$ suppresses 5-LOX expression and induces 15-lipoxygenase (15-LOX). This is a key step in shifting the balance of mediators away from inflammation to resolution.

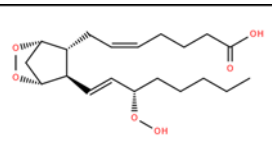
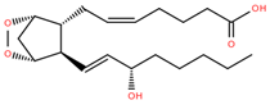
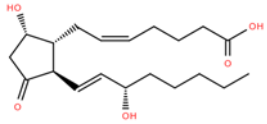
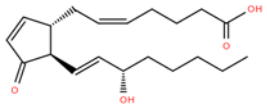
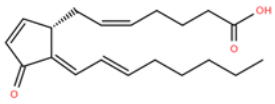
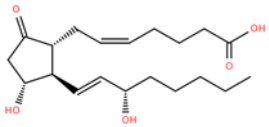
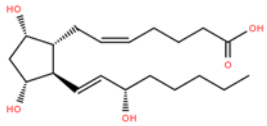
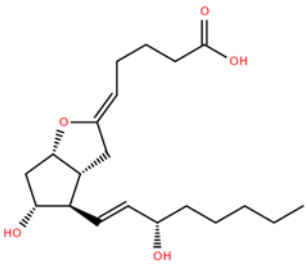
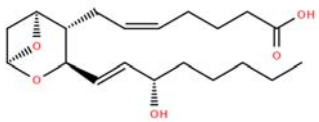
Figure 7. Interaction between the prostacyclin and nitric oxide systems. Thromboxane $A_2$ and prostaglandin (PG)$I_2$ (also called prostacyclin typically oppose one another's action. Platelets produce $TXA_2$ while endothelial cells produce $PGI_2$. $TXA_2$ causes smooth muscle to contract which $PGI_2$ causes them to relax. Endothelial cells also produce nitric oxide (NO) through the endothelial nitric oxide synthase (eNOS). When oxidative stress is excessive superoxide ($O2^{-\cdot}$) combines with NO to produce peroxynitrite ($ONOO^-$). Peroxynitrite activates cyclooxygenase (COX) but inhibits PGI synthase (PGIS). Thus, $PGI_2$ concentrations fall and $TXA_2$ predominates. This favours smooth muscle contraction and proliferation. Furthermore, he inhibition of PGIS results in accumulation of $PGH_2$ which is believed to act via the TP receptor to induce smooth muscle contraction.

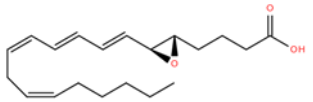
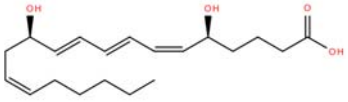
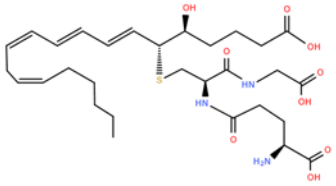
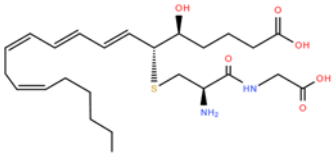
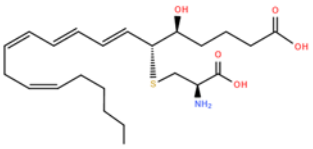
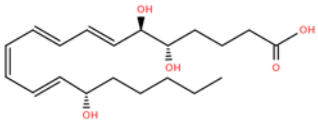
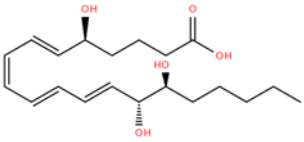
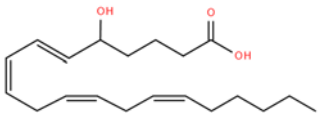
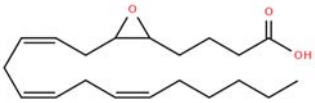
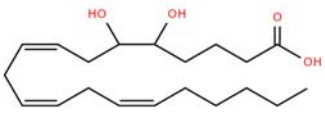
Figure 8. Summary of the multiple actions of eicosanoids in allergic inflammation and asthma. Prostaglandin (PG)$D_2$ and the 4-series leukotrienes (LTs), especially the cysteinyl-LTs are mediators of allergic inflammation. $PGE_2$ acts to modify T-lymphocyte phenotypes in a way that predisposes to allergic inflammation. Through activation of regulatory T-cells (Tregs) $PGE_2$ suppresses T helper 1 (Th1) lymphocytes. These produce interferon (IFN)-γ which normally restricts T helper 2 (Th2) lymphocytes. Without the inhibition of IFN-γ Th2 cells produce interleukin (IL)-4 and IL-13 which promote pro-allergic immunoglobulin E (IgE) production by B-cells. Th2 cells produce other cytokines like IL-5, which activates eosinophils, that also act to promote the allergic response.

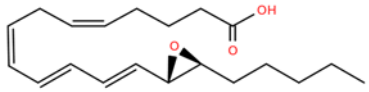
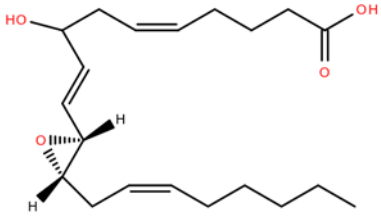
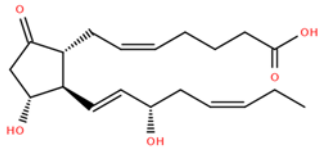
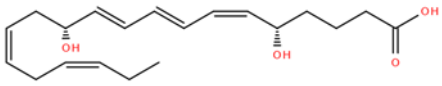
Figure 9. Sites of action of the principal inhibitors of eicosanoid synthesis and action. COX, cyclooxygenase; DHET, dihydroxyeicosatrienoic acid; EET, epoxyeicosatrienoic acid; FLAP,

5-lipoxygease activating protein; LOX, lipoxygenase; LT, leukotriene; PG, prostaglandin; sEH, soluble epoxide hydrolase; TX, thromboxane.

Table 1. The structures of a selection of eicosanoids.

| Common name | Systematic name | Structure |
|---|---|---|
| $PGG_2$ | 9S,11R-epidioxy-15S-hydroperoxy-5Z,13E-prostadienoic acid |  |
| $PGH_2$ | 9S,11R-epidioxy-15S-hydroxy-5Z,13E-prostadienoic acid |  |
| $PGD_2$ | 9S,15S-dihydroxy-11-oxo-5Z,13E-prostadienoic acid |  |
| $PGJ_2$ | 11-oxo-15S-hydroxy-5Z,9,13E-prostatrienoic acid |  |
| 15-deoxy-$PGJ_2$ | 11-oxo-5Z,9,12E,14E-prostatetraenoic acid |  |
| $PGE_2$ | 9-oxo-11R,15S-dihydroxy-5Z,13E-prostadienoic acid |  |
| $PGF_{2a}$ | 9S,11R,15S-trihydroxy-5Z,13E-prostadienoic acid |  |
| $PGI_2$ | 6,9S-epoxy-11R,15S-dihydoxy-5Z,13E-prostadienoic acid |  |
| $TXA_2$ | 9S,11S-epoxy,15S-hydroxy-thromboxa-5Z,13E-dien-1-oic acid |  |

| | | |
|---|---|---|
| $LTA_4$ | 5S,6S-epoxy-7E,9E,11Z,14Z-eicosatetraenoic acid |  |
| $LTB_4$ | 5S,12R-dihydroxy-6Z,8E,10E,14Z-eicosatetraenoic acid |  |
| $LTC_4$ | 5S-hydroxy,6R-(S-glutathionyl),7E,9E,11Z,14Z-eicosatetraenoic acid |  |
| $LTD_4$ | 5S-hydroxy-6R-(S-cysteinylglycinyl)-7E,9E,11E,14Z-eicosatetraenoic acid |  |
| $LTE_4$ | 5S-hydroxy,6R-(S-cysteinyl),7E,9E,11Z,14Z-eicosatetraenoic acid |  |
| $LXA_4$ | 5S,6R,15S-trihydroxy-7E,9E,11Z,13E-eicosatetraenoic acid |  |
| $LXB_4$ | 5S,14R,15S-trihydroxy-6E,8Z,10E,12E-eicosatetraenoic acid |  |
| 5-HETE | 5-hydroxy-6E,8Z,11Z,14Z-eicosatetraenoic acid |  |
| 5,6-EET | 5,6-epoxy-8Z,11Z,14Z-eicosatrienoic acid |  |
| 5,6-DHET | 5,6-dihydroxy-8Z,11Z,14Z-eicosatrienoic acid |  |

| | | |
|---|---|---|
| 14,15-LTA$_4$ (eoxin A$_4$) | 14S,15S-epoxy-5Z,8Z,10E,12E-eicosatetraenoic acid |  |
| Hepoxilin A$_3$ | 8-hydroxy-11S,12S-epoxy-5Z,14Z,9E-eicosatrienoic acid |  |
| PGE$_3$ | 9-oxo-11R,15S-dihydroxy-5Z,13E,17Z-prostatrienoic acid |  |
| LTB$_5$ | 5S,12S-dihydroxy-6Z,8E,14Z,17Z-eicosapentanenoic acid |  |

DHET, dihydroxyeicosatrienoic acid; EET, epoxyeicosatriencoic acid; HETE, hydroxyeicosatetraenoic acid; LT, leukotriene; LX, lipoxin; PG, prostaglandin; TX, thromboxane

Table 2. G-protein coupled eicosanoid receptors, their ligands and their signalling systems.

| Receptor | Ligand preference | G-protein type | Signalling |
|---|---|---|---|
| $DP_1$ | $PGD_2 >> PGE_2 >> PGF_{2\alpha} > PGI_2 = TXA_2$ | $G_s$ | ↑ Adenylate cyclase activity |
| $DP_2$ | $PGD_2 >> PGF_{2\alpha} = PGE_2 > PGI_2 = TXA_2$ | $G_i/G_o$ | ↓ Adenylate cyclase activity |
| $EP_1$ | $PGE_2 > PGF_{2\alpha}$ | $G_q/G_{11}$ | ↑ Phospholipase C activity |
| $EP_2$ | $PGE_2 > PGF_{2\alpha} = PGI_2 > PGD_2 = TXA_2$ | $G_s$ | ↑ Adenylate cyclase activity |
| $EP_3$ | $PGE_2 > PGF_{2\alpha} = PGI_2 > PGD_2 = TXA_2$ | $G_i/G_o$ | ↓ Adenylate cyclase activity |
| $EP_4$ | $PGE_2 > PGF_{2\alpha} = PGI_2 > PGD_2 = TXA_2$ | $G_s$ | ↑ Adenylate cyclase activity |
| FP | $PGF_{2\alpha} > PGD_2 > PGE_2 > PGI_2 = TXA_2$ | $G_q/G_{11}$ | ↑ Phospholipase C activity |
| IP | $PGI_2 > PGE_2 >> PGF_{2\alpha} = PGD_2 > TXA_2$ | $G_s$ | ↑ Adenylate cyclase activity |
| TP | $TXA_2 > PGH_2 > > PGD_2 = PGE_2 = PGF_{2\alpha}$ | $G_q/G_{11}$ | ↑ Phospholipase C activity |
| $BLT_1$ | $LTB_4$ | $G_i/G_o$ and $G_q/G_{11}$ | ↓ Adenylate cyclase activity<br>↑ Phospholipase C activity |
| $BLT_2$ | 12 hydroxyheptadecatrienoic acid > $LTB_4$ > many HETEs | $G_i/G_o$ | ↓ Adenylate cyclase activity |
| $CysLT_1$ | $LTD_4 > LTC_4 > LTE_4$ | $G_q/G_{11}$ | ↑ Phospholipase C activity |
| $CysLT_2$ | $LTC_4 \geq LTD_4 > LTE_4$ | $G_q/G_{11}$ | ↑ Phospholipase C activity |
| $CysLT_3$* | $LTE_4$ | $G_q/G_{11}$ | ↑ Phospholipase C activity |
| GPR17** | $LTC_4 > LTD_4 > LTE_4$ | $G_i/G_o$ | ↓ Adenylate cyclase activity |
| $P2Y_{12}$*** | $LTE_4$ | Gi/Go | ↓ Adenylate cyclase activity |
| ALX | $LXA_4$ = Asprin-triggered-$LXA_4$ = resolvin D1 > $LTC_4$ > $LTD_4$ | $G_i/G_o$ and $G_q/G_{11}$ | ↓ Adenylate cyclase activity<br>↑ Phospholipase C activity |

*preferentially binds a-ketoglutaric acid

**preferentially binds ATP and UDP-sugars

***preferentially binds ADP and ATP