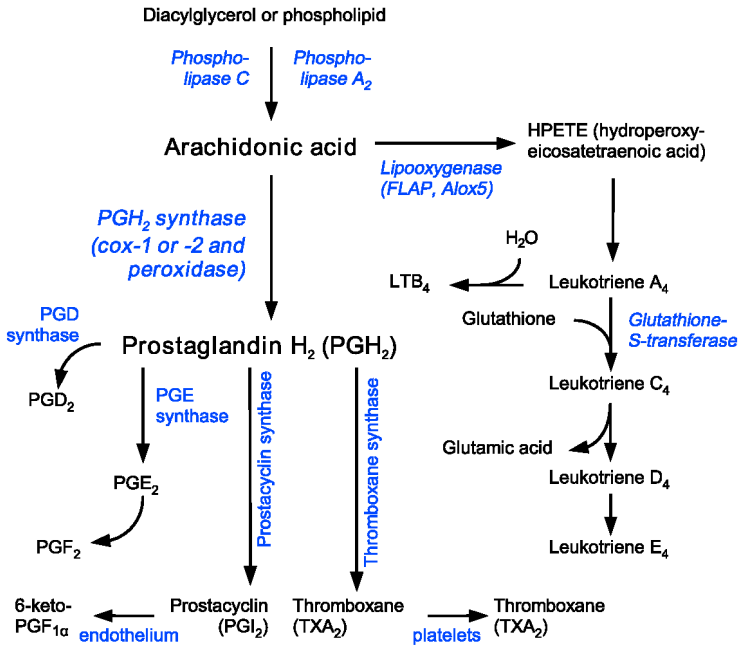
Eicosanoid

In biochemistry, **eicosanoids** (preferred IUPAC name **icosanoids**) are signaling molecules made by oxidation of twenty-carbon essential fatty acids, (EFAs). They exert complex control over many bodily systems, mainly in inflammation or immunity, and as messengers in the central nervous system. The networks of controls that depend upon eicosanoids are among the most complex in the human body.



Pathways in biosynthesis of **eicosanoid**s from arachidonic acid: there are parallel paths from EPA & DGLA.

Eicosanoids derive from either omega-3 (ω-3) or omega-6 (ω-6) EFAs. The ω-6 eicosanoids are generally pro-inflammatory; ω-3s are much less so. The amounts and balance of these fats in a person's diet will affect the body's eicosanoid-controlled functions, with effects on cardiovascular disease, triglycerides, blood pressure, and arthritis. Anti-inflammatory drugs such as aspirin and other NSAIDs act by downregulating eicosanoid synthesis.

There are four families of eicosanoids—the prostaglandins, prostacyclins, the thromboxanes and the leukotrienes. For each, there are two or three separate series, derived either from an ω-3 or ω-6 EFA. These series' different activities largely explain the health effects of ω-3 and ω-6 fats.[1][2][3][4]

Nomenclature

See related detail at Essential Fatty Acid Interactions—Nomenclature

"Eicosanoid" (*eicosa-*, Greek for "twenty"; *see icosahedron*) is the collective term[5] for oxygenated derivatives of three different 20-carbon essential fatty acids:

- Eicosapentaenoic acid (**EPA**), an ω-3 fatty acid with 5 double bonds;
- Arachidonic acid (**AA**), an ω-6 fatty acid, with 4 double bonds;
- Dihomo-gamma-linolenic acid (**DGLA**), an ω-6, with 3 double bonds.

Current usage limits the term to the leukotrienes (**LT**) and three types of prostanoids—prostaglandins (**PG**) prostacyclins (**PGI**), and thromboxanes (**TX**). This is the definition used in this article. However, several other classes can technically be termed eicosanoid, including the hepoxilins, resolvins, isofurans, isoprostanes, lipoxins, epi-lipoxins, epoxyeicosatrienoic acids (EETs) and endocannabinoids. LTs and prostanoids are sometimes termed 'classic eicosanoids'[6][7][8] in contrast to the 'novel', 'eicosanoid-like' or 'nonclassic eicosanoids'.[9][10][11][12]

A particular eicosanoid is denoted by a four-character abbreviation, composed of:

- Its two letter abbreviation (above),[13]
- One A-B-C sequence-letter;[14] and
- A subscript, indicating the number of double bonds.

Examples are:

- The EPA-derived prostanoids have three double bonds, (e.g. PGG_3, PGH_3, PGI_3, TXA_3) while its leukotrienes have five, (LTB_5).
- The AA-derived prostanoids have two double bonds, (e.g. PGG_2, PGH_2, PGI_2, TXA_2) while its leukotrienes have four, (LTB_4).

Furthermore, stereochemistry may differ among the pathways, indicated by Greek letters, e.g. for ($PGF_{2\alpha}$).

Biosynthesis

Two families of enzymes catalyze fatty acid oxygenation to produce the eicosanoids:

- Cyclooxygenase, or COX, generates the prostanoids.
- Lipoxygenase, or LOX, in several forms. 5-lipoxygenase (5-LO) generates the leukotrienes.

Eicosanoids are not stored within cells, but are synthesized as required. They derive from the fatty acids that make up the cell membrane and nuclear membrane.

Eicosanoid biosynthesis begins when cell is activated by mechanical trauma, cytokines, growth factors or other stimuli. (The stimulus may even be an eicosanoid from a neighboring cell; the pathways are complex.) This triggers the release of a phospholipase at the cell membrane. The phospholipase travels to the nuclear membrane. There, the phospholipase catalyzes ester hydrolysis of phospholipid (by A_2) or diacylglycerol (by phospholipase C). This frees a 20-carbon essential fatty acid. This hydrolysis appears to be the rate-determining step for eicosanoid formation.

The fatty acids may be released by any of several phospholipases. Of these, type IV cytosolic phospholipase A_2 ($cPLA_2$) is the key actor, as cells lacking $cPLA_2$ are generally devoid of eicosanoid synthesis. The phospholipase $cPLA_2$ is specific for phospholipids that contain AA, EPA or GPLA at the SN2 position. Interestingly, $cPLA_2$ may also release the lysophospholipid that becomes platelet-activating factor.[15]

Peroxidation and reactive oxygen species

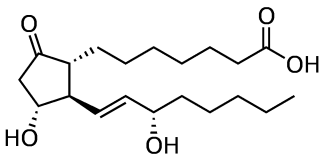
Next, the free fatty acid is oxygenated along any of several pathways; see the *Pathways* table. The eicosanoid pathways (*via* lipoxygenase or COX) add molecular oxygen (O_2). Although the fatty acid is symmetric, the resulting eicosanoids are chiral; the oxidation proceeds with high stereospecificity.

The oxidation of lipids is hazardous to cells, particularly when close to the nucleus. There are elaborate mechanisms to prevent unwanted oxidation. COX, the lipoxygenases and the phospholipases are tightly controlled—there are at least eight proteins activated to coordinate generation of leukotrienes. Several of these exist in multiple isoforms.[4]

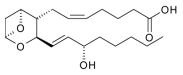
Oxidation by either COX or lipoxygenase releases reactive oxygen species (ROS) and the initial products in eicosanoid generation are themselves highly reactive peroxides. LTA_4 can form adducts with tissue DNA. Other reactions of lipoxygenases generate cellular damage; murine models implicate 15-lipoxygenase in the pathogenesis of atherosclerosis.[16][17] The oxidation in eicosanoid generation is compartmentalized; this limits the peroxides' damage. The enzymes which are biosynthetic for eicosanoids (e.g. glutathione-S-transferases, epoxide hydrolases and carrier proteins) belong to families whose functions are largely involved with cellular detoxification. This suggests that eicosanoid signaling may have evolved from the detoxification of ROS.

The cell must realize some benefit from generating lipid hydroperoxides close-by its nucleus. PGs and LTs may signal or regulate DNA-transcription there; LTB_4 is ligand for PPARα.[2] *(See diagram at PPAR).*

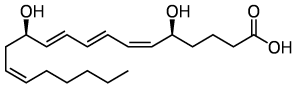
Structures of Selected Eicosanoids



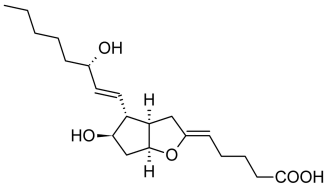
Prostaglandin E_1. The 5-member ring is characteristic of the class.



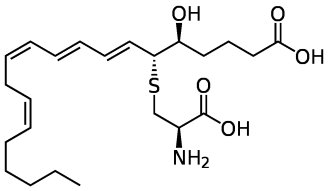
Thromboxane A_2. Oxygens have moved into the ring.



Leukotriene B_4. Note the 3 conjugated double bonds.



Prostacyclin I_2. The second ring distinguishes it from the prostaglandins.



Leukotriene E_4, an example of a cysteinyl leukotriene.

Prostanoid pathways

See Prostanoid#Biosynthesis.

Cyclooxygenase (*COX*) catalyzes the conversion of the free essential fatty acids to prostanoids by a two-step process. First, two molecules of O_2 are added as two peroxide linkages, and a 5-member carbon ring is forged near the middle of the fatty acid chain. This forms the short-lived, unstable intermediate Prostaglandin G (PGG). Next, one of the peroxide linkages sheds a single oxygen, forming PGH. *(See diagrams and more detail of these steps at Cyclooxygenase).*

All three classes of prostanoids originate from PGH. All have distinctive rings in the center of the molecule. They differ in their structures. The PGH compounds (parents to all the rest) have a 5-carbon ring, bridged by two oxygens (a peroxide.) As the example in *Structures of Selected Eicosanoids* figure shows, the derived prostaglandins contain a single, unsaturated 5-carbon ring. In prostacyclins, this ring is conjoined to another oxygen-containing ring. In thromboxanes the ring becomes a 6-member ring with one oxygen. The leukotrienes do not have rings. *(See more detail, including the enzymes involved, in diagrams at Prostanoid.)*

Several drugs lower inflammation by blocking prostanoid synthesis; see detail at Cyclooxygenase, Aspirin and NSAID.

Leukotriene pathways

See Leukotriene#Biosynthesis.

The enzyme 5-lipoxygenase (5-LO) uses 5-lipoxygenase activating protein (FLAP) to convert arachidonic acid into 5-hydroperoxyeicosatetraenoic acid (5-HPETE), which spontaneously reduces to 5-hydroxyeicosatetraenoic acid (5-HETE). The enzyme LTA synthase acts on 5-HPETE to convert it into leukotriene A_4 (LTA_4), which may be converted into LTB_4 by the enzyme leukotriene A4 epoxide hydrolase. Eosinophils, mast cells, and alveolar macrophages use the enzyme leukotriene C4 synthase to conjugate glutathione with LTA_4 to make LTC_4, which is transported outside the cell, where a glutamic acid moiety is removed from it to make LTD_4. The leukotriene LTD_4 is then cleaved by dipeptidases to make LTE_4. The leukotrienes LTC_4, LTD_4 and LTE_4 all contain cysteine and are collectively known as the cysteinyl leukotrienes.

Function and pharmacology

Metabolic actions of selected prostanoids and leukotrienes†[15]

PGD_2	Promotion of sleep	TXA_2	Stimulation of platelet aggregation; vasoconstriction
PGE_2	Smooth muscle contraction; inducing pain, heat, fever; bronchoconstriction	15d-PGJ_2	Adipocyte differentiation
$PGF_{2\alpha}$	Uterine contraction	LTB_4	Leukocyte chemotaxis
PGI_2	Inhibition of platelet aggregation; vasodilation; embryo implantation	Cysteinyl-LTs	Anaphylaxis; bronchial smooth muscle contraction.
†Shown eicosanoids are AA-derived; EPA-derived generally have weaker activity			

Eicosanoids exert complex control over many bodily systems, mainly in inflammation or immunity, and as messengers in the central nervous system. They are found in most living things. In humans, eicosanoids are local hormones that are released by most cells, act on that same cell or nearby cells (i.e., they are autocrine and paracrine mediators), and then are rapidly inactivated.

Eicosanoids have a short half-life, ranging from seconds to minutes. Dietary antioxidants inhibit the generation of some inflammatory eicosanoids, e.g. trans-resveratrol against thromboxane and some leukotrienes.[18] Most eicosanoid receptors are members of the G protein-coupled receptor superfamily; see the *Receptors* table or the article eicosanoid receptors.

Receptors: There are specific receptors for all eicosanoids (see also: eicosanoid receptors)

Leukotrienes:

- CysLT1 (Cysteinyl leukotriene receptor type 1)
- CysLT2 (Cysteinyl leukotriene receptor type 2)
- BLT1 (Leukotriene B4 receptor)

Prostanoids:

- PGD_2: DP-(PGD_2)
- PGE_2:
  - EP_1-(PGE_2)
  - EP_2-(PGE_2)
  - EP_3-(PGE_2)
  - EP_4-(PGE_2)
- $PGF_{2\alpha}$: FP-($PGF_{2\alpha}$)
- PGI_2 (prostacyclin): IP-(PGI_2)
- TXA_2 (thromboxane): TP-(TXA_2)

The ω-3 and ω-6 series

> The reduction in AA-derived eicosanoids and the diminished activity of the alternative products generated from ω-3 fatty acids serve as the foundation for explaining some of the beneficial effects of greater ω-3 intake.
>
> —Kevin Fritsche, Fatty Acids as Modulators of the Immune Response[19]

Arachidonic acid (AA; 20:4 ω-6) sits at the head of the 'arachidonic acid cascade'—more than twenty different eicosanoid-mediated signaling paths controlling a wide array of cellular functions, especially those regulating inflammation, immunity and the central nervous system.[3]

In the inflammatory response, two other groups of dietary essential fatty acids form cascades that parallel and compete with the arachidonic acid cascade. EPA (20:5 ω-3) provides the most important competing cascade. DGLA (20:3 ω-6) provides a third, less prominent cascade. These two parallel cascades soften the inflammatory effects of AA and its products. Low dietary intake of these less-inflammatory essential fatty acids, especially the ω-3s, has been linked to several inflammation-related diseases, and perhaps some mental illnesses.

The U.S. National Institutes of Health and the National Library of Medicine state that there is 'A' level evidence that increased dietary ω-3 improves outcomes in hypertriglyceridemia, secondary cardiovascular disease prevention and hypertension. There is 'B' level evidence ('good scientific evidence') for increased dietary ω-3 in primary prevention of cardiovascular disease, rheumatoid arthritis and protection from ciclosporin toxicity in organ transplant patients. They also note more preliminary evidence showing that dietary ω-3 can ease symptoms in several psychiatric disorders.[20]

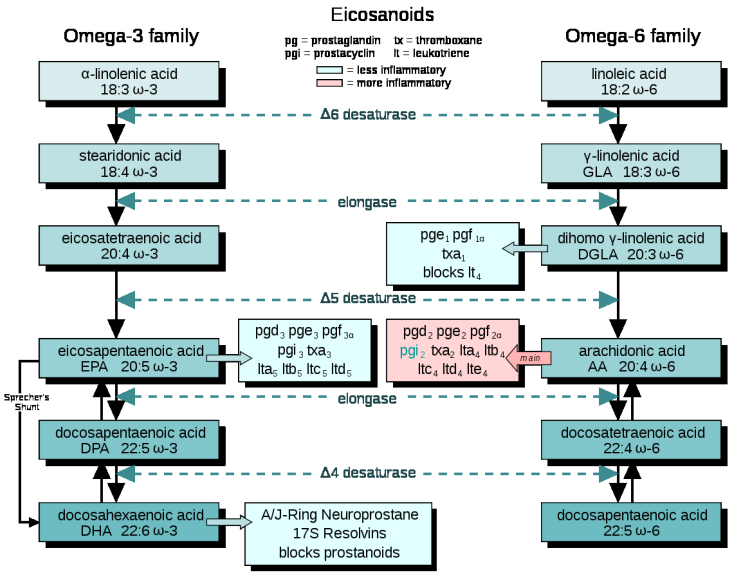
Besides the influence on eicosanoids, dietary polyunsaturated fats modulate immune response through three other molecular mechanisms. They (a) alter membrane composition and function, including the composition of lipid rafts; (b) change cytokine biosynthesis and (c) directly activate gene transcription.[19] Of these, the action on eicosanoids is the best explored.

Mechanisms of ω-3 action

The eicosanoids from AA generally promote inflammation. Those from EPA and from GLA (*via* DGLA) are generally less inflammatory, or inactive, or even anti-inflammatory. The figure shows the ω-3 and -6 synthesis chains, along with the major eicosanoids from AA, EPA and DGLA.

Dietary ω-3 and GLA counter the inflammatory effects of AA's eicosanoids in three ways, along the eicosanoid pathways:

- *Displacement*—Dietary ω-3 decreases tissue concentrations of AA, so there is less to form ω-6 eicosanoids.



EFA sources: Essential fatty acid production and metabolism to form eicosanoids. At each step, the ω-3 and ω-6 cascades compete for the enzymes.

- *Competitive inhibition*—DGLA and EPA compete with AA for access to the cyclooxygenase and lipoxygenase enzymes. So the presence of DGLA and EPA in tissues lowers the output of AA's eicosanoids.
- *Counteraction*—Some DGLA and EPA derived eicosanoids counteract their AA derived counterparts.

Role in inflammation

Since antiquity, the cardinal signs of inflammation have been known as: calor (warmth), dolor (pain), tumor (swelling) and rubor (redness). The eicosanoids are involved with each of these signs.

Redness—An insect's sting will trigger the classic inflammatory response. Short acting vasoconstrictors —TXA_2—are released quickly after the injury. The site may momentarily turn pale. Then TXA_2 mediates the release of the vasodilators PGE_2 and LTB_4. The blood vessels engorge and the injury reddens.
Swelling—LTB_4 makes the blood vessels more permeable. Plasma leaks out into the connective tissues, and they swell. The process also loses pro-inflammatory cytokines.
Pain—The cytokines increase COX-2 activity. This elevates levels of PGE_2, sensitizing pain neurons.
Heat—PGE_2 is also a potent pyretic agent. Aspirin and NSAIDS—drugs that block the COX pathways and stop prostanoid synthesis—limit fever or the heat of localized inflammation.

Pharmacy: Eicosanoid, eicosanoid analogs and receptor agonists/antagonists used as medicines

Medicine	Type	Medical condition or use
Alprostadil	PGE_1	Erectile dysfunction, maintaining a patent ductus arteriosus in the fetus
Beraprost	PGI_1 analog	Pulmonary hypertension, avoiding reperfusion injury
Bimatoprost	PG analog	Glaucoma, ocular hypertension
Carboprost	PG analog	Labor induction, abortifacient in early pregnancy
Dinoprostone	PGE_2	Labor induction
Iloprost	PGI_2 analog	Pulmonary arterial hypertension
Latanoprost	PG analog	Glaucoma, ocular hypertension
Misoprostol	PGE_1 analog	Stomach ulcers, labor induction, abortifacient
Montelukast	LT receptor antagonist	Asthma, seasonal allergies
Travoprost	PG analog	Glaucoma, ocular hypertension
Treprostinil	PGI analog	Pulmonary hypertension
U46619	Longer lived TX analog	Research only
Zafirlukast	LT receptor antagonist	Asthma

Action of prostanoids

Main articles: Prostaglandin, Prostacyclin and Thromboxane

Prostanoids mediate local symptoms of inflammation: vasoconstriction or vasodilation, coagulation, pain and fever. Inhibition of cyclooxygenase, specifically the inducible COX-2 isoform, is the hallmark of NSAIDs (non-steroidal anti-inflammatory drugs), such as aspirin. COX-2 is responsible for pain and inflammation, while COX-1 is responsible for platelet clotting actions.

Prostanoids activate the $PPAR_{\gamma}$ members of the steroid/thyroid family of nuclear hormone receptors, directly influencing gene transcription.[21]

Action of leukotrienes

Leukotrienes play an important role in inflammation. There is a neuroendocrine role for LTC_4 in luteinizing hormone secretion.[22] LTB_4 causes adhesion and chemotaxis of leukocytes and stimulates aggregation, enzyme release, and generation of superoxide in neutrophils.[23] Blocking leukotriene receptors can play a role in the management of inflammatory diseases such as asthma (by the drugs montelukast and zafirlukast), psoriasis, and rheumatoid arthritis.

The slow reacting substance of anaphylaxis comprises the cysteinyl leukotrienes. These have a clear role in pathophysiological conditions such as asthma, allergic rhinitis and other nasal allergies, and have been implicated in atherosclerosis and inflammatory gastrointestinal diseases.[24] They are potent bronchoconstrictors, increase vascular permeability in postcapillary venules, and stimulate mucus secretion. They are released from the lung tissue of asthmatic subjects exposed to specific allergens and play a pathophysiological role in immediate hypersensitivity reactions.[23] Along with PGD, they function in effector cell trafficking, antigen presentation, immune cell activation, matrix deposition, and fibrosis.[25]

History

In 1930, gynecologist Raphael Kurzrok and pharmacologist Charles Leib characterized prostaglandin as a component of semen. Between 1929 and 1932, Burr and Burr showed that restricting fat from animal's diets led to a deficiency disease, and first described the essential fatty acids.[26] In 1935, von Euler identified prostaglandin. In 1964, Bergström and Samuelsson linked these observations when they showed that the "classical" eicosanoids were derived from arachidonic acid, which had earlier been considered to be one of the essential fatty acids.[27] In 1971, Vane showed that aspirin and similar drugs inhibit prostaglandin synthesis.[28] Von Euler received the Nobel Prize in medicine in 1970, which Samuelsson, Vane, and Bergström also received in 1982. E. J. Corey received it in chemistry in 1990 largely for his synthesis of prostaglandins.

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[13] Prostacyclin—PGI—was previously classified as prostaglandin and retains its old identifier.

[14] Eicosanoids with different letters have placement of double-bonds and different functional groups attached to the molecular skeleton. Letters indicate roughly the order the eicosanoids were first described in the literature. For diagrams for PG [A–H] see Cyberlipid Center. "Prostanoids" (http://www.cyberlipid.org/prost1/pros0001.htm). . Retrieved 2007-02-05.

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