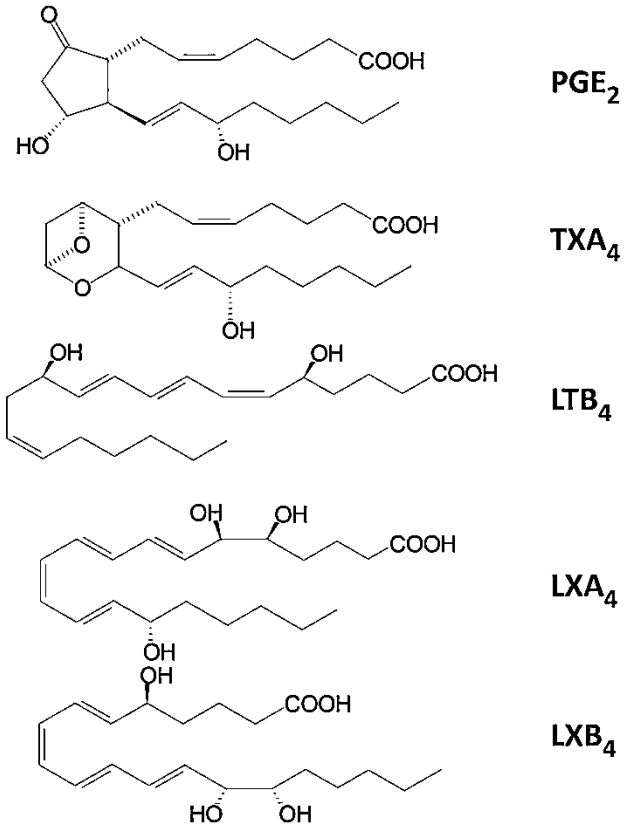
Introduction to the Eicosanoids

The eicosanoids consist 20 carbon unit molecules and named as: prostaglandins (PG), thromboxanes (TX), leukotrienes (LT) and lipoxins (LX). The PGs and TXs are collectively identified as prostanoids. The nomenclature of the prostanoids includes a subscript number which refers to the number of carbon-carbon double bonds that exist in the molecule. The majority of the biologically active prostaglandins and thromboxanes are referred to as **series 2** molecules due to the presence of two carbon-carbon double bonds. The predominant leukotrienes are **series 4** molecules due to the presence of four carbon-carbon double bonds. There are, however, important **series 1** prostaglandins and thromboxanes as described below.

Prostaglandins were originally shown to be synthesized in the prostate gland, thromboxanes from platelets (thrombocytes) and leukotrienes from leukocytes, hence the derivation of their names. The lipoxins are inflammation resolving eicosanoids synthesized through **lipox**ygenase **in**teractions (hence the derivation of the name). Lipoxins are potent inflammation modulating eicosanoid derivatives and their synthesis can be increased in response to ingestion of aspirin.

The eicosanoids produce a wide range of biological effects on inflammatory responses (predominantly those of the joints, skin and eyes), on the intensity and duration of pain and fever, and on reproductive function (including the induction of labor). They also play important roles in inhibiting gastric acid secretion, regulating blood pressure through vasodilation or constriction, and inhibiting or activating platelet aggregation and thrombosis.

Structures of Representative Clinically Relevant Eicosanoids

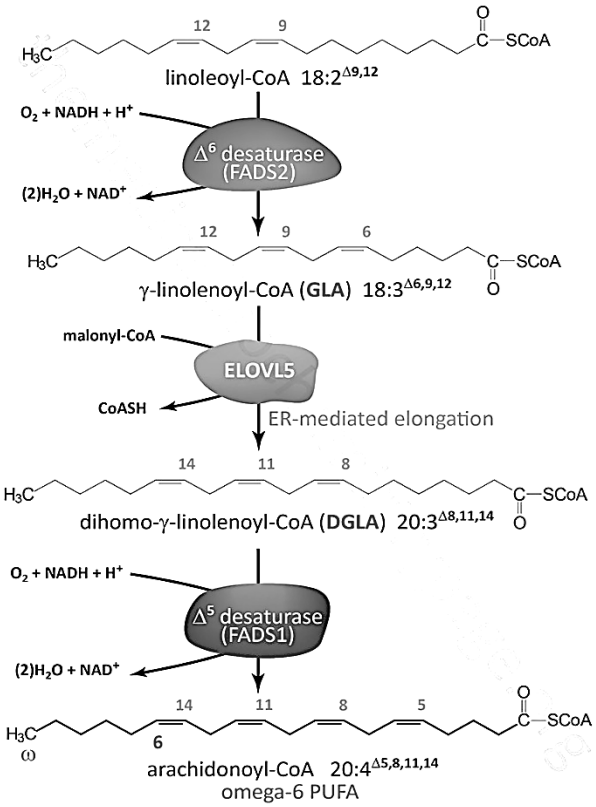


The principal eicosanoids of biological significance to humans are a group of molecules derived from the 20:4 (20 carbons: 4 sites of unsaturation) fatty acid, arachidonic acid. The major source of arachidonic acid is through its release from membrane phospholipids. Within cell membranes, arachidonic acid resides predominantly at the C–2 position of

phospholipids (primarily phosphatidylinositol-4,5-bisphosphate, PIP_2) and is released from there upon the activation of the lipid hydrolase phospholipase A_2, PLA_2.

The immediate dietary precursor of arachidonic acid is the 18-carbon essential fatty acid, linoleic acid. Linoleic acid is converted to arachidonic acid through the steps outlined in the Figure to the right.

The activity of the Δ^6-desaturase (D6D), which produces GLA, is slow and can be further compromised due to nutritional deficiencies as well as during inflammatory conditions. The D6D enzyme is officially called fatty acid desaturase 2 which is encoded by the FADS2 gene. GLA is converted to DGLA via the microsomal (ER) fatty acid elongation pathway. DGLA is subsequently further unsaturated to arachidonic acid by the enzyme Δ^5-desaturase (D5D). The D5D enzyme is officially called fatty acid desaturase 1 which is encoded by the FADS1 gene. Like the Δ^6-desaturase, the activity of the Δ^5-desaturase is limiting in arachidonic acid synthesis and its activity is also influenced by diet and environmental factors.



Arachidonic acid synthesis. Synthesis of arachidonic acid, a polyunsaturated fatty acid (PUFA) of 20 carbon atoms with four sites of unsaturation, begins with the CoA-activated form of linoleic acid (linoleoyl-CoA) which is an 18 carbon fatty acid with two sites of unsaturation. The process of arachidonic acid synthesis, therefore, involves both elongation and two separate desaturation steps.

The activity of the D5D and D6D enzymes is also compromised by the consumption of pro-inflammatory omega-6 fatty acids, such as the essential fatty acid linoleic acid and arachidonic acid, as is typical in the Western-style diet. Consumption of alcohol has also been shown to reduce the level of D6D activity. In addition, hyperglycemia and hypercholesterolemia are both known to interfere with the activity of D5D and D6D. Due to the limited activity of the Δ^5-desaturase most of the DGLA formed from GLA is inserted into membrane phospholipids at the same C-2 position as for arachidonic acid. As discussed in detail below, DGLA serves as a precursor for the series-1 eicosanoids which exert opposing biological effects to the series-2 eicosanoids derived from arachidonic acid.

Diets containing sources of GLA have been shown have distinct cardiovascular benefit similar to diets rich in omega-3 polyunsaturated fatty acids (PUFAs) such as is found in cold water fishes, and the blue-green algaes (cyanobacteria).

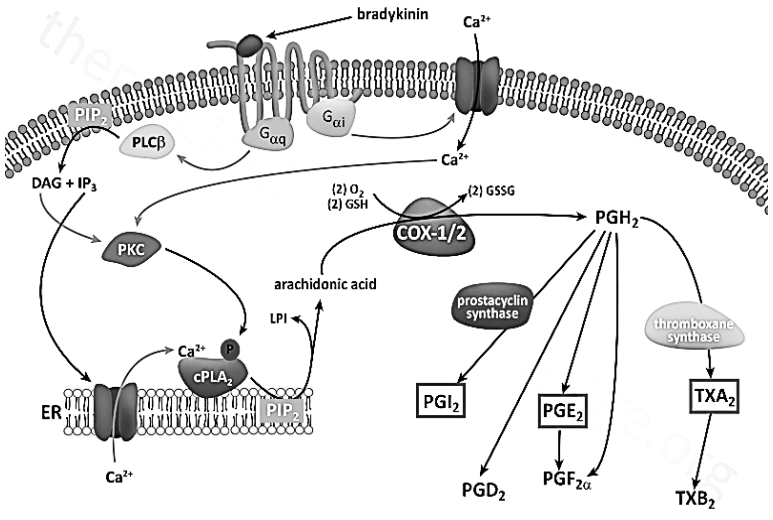
Eicosanoid Synthesis

All mammalian cells except erythrocytes synthesize eicosanoids. These molecules are extremely potent, able to cause profound physiological effects at very dilute concentrations. All eicosanoids function locally at the site of synthesis, through *receptor-mediated G-protein linked signaling pathways*.

Two main pathways are involved in the biosynthesis of eicosanoids, the cyclic and the linear pathways. The prostaglandins and thromboxanes are synthesized by the cyclic pathway, the leukotrienes are synthesized by the linear pathway.

The cyclic pathway is initiated through the action of prostaglandin synthase, PGS. This enzyme possesses two activities, cyclooxygenase (COX) and peroxidase. There are two forms of the COX activity in humans, COX-1 and COX-2. COX-1 (PGS-1) is expressed constitutively in gastric mucosa, kidney, platelets, and vascular endothelial cells. COX-2 (PGS-2) is inducible and is expressed in macrophages and monocytes in response to inflammation. The primary triggers for COX-2 induction in monocytes and macrophages are platelet-activating factor, PAF and interleukin-1, IL-1. Both COX-1 and COX-2 catalyze the 2-step conversion of arachidonic acid to PGG_2 and then to PGH_2. The gene encoding COX-1 is identified as the PTGS1 gene and that encoding COX-2 is the PTGS2 gene.

Synthesis of the clinically relevant prostaglandins and thromboxanes from arachidonic acid. Hormone receptors are coupled to G-protein activation with the net effect that there is increased intracellular calcium and activation of PKC. Both PKC phosphorylation and the Ca^{2+} ions activate the ER membrane-associated $cPLA_2$ isoforms which, when activated, hydrolyze arachidonic acid from PIP_2. Arachidonic acid is converted to PGH_2 via the action of the bi-functional enzymes COX-1 and COX-2. The prostaglandins are identified as PG and the thromboxanes as TX. to PGD_2. Prostacyclin (PGI_2) is synthesized from PGH_2 via the action of prostacyclin synthase (encoded by the PTGIS gene). The principal thromboxane (TXA_2) is derived from PGH_2 via the action of thromboxane A synthase 1 encoded by the TBXAS1 gene. The three most physiologically significant cyclic eicosanoids are enclosed in boxes. The subscript 2 in each molecule refers to the number of carbon-carbon double bonds present.



Leukotriene Synthesis

The linear pathway is initiated through the action of arachidonate lipoxygenases (LOXs) of which there are three forms, 5-LOX, 12-LOX and 15-LOX. The official names for these three enzymes are arachidonate 5-lipoxygenase, arachidonate 12-lipoxygenase, and arachidonate 15-lipoxygenase. It is 5-LOX that gives rise to the leukotrienes. The leukotrienes are synthesized by several different cell types including white blood cells (leukocytes, hence the derivation of the name of the compounds), mast cells, lung, spleen, brain and heart. The activities of 12-LOX and 15-LOX are involved in the synthesis of the lipoxins.