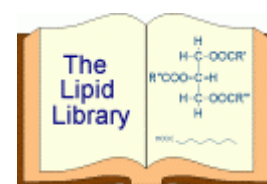


# PROSTANOIDS - PROSTAGLANDINS, PROSTACYCLINS and THROMBOXANES

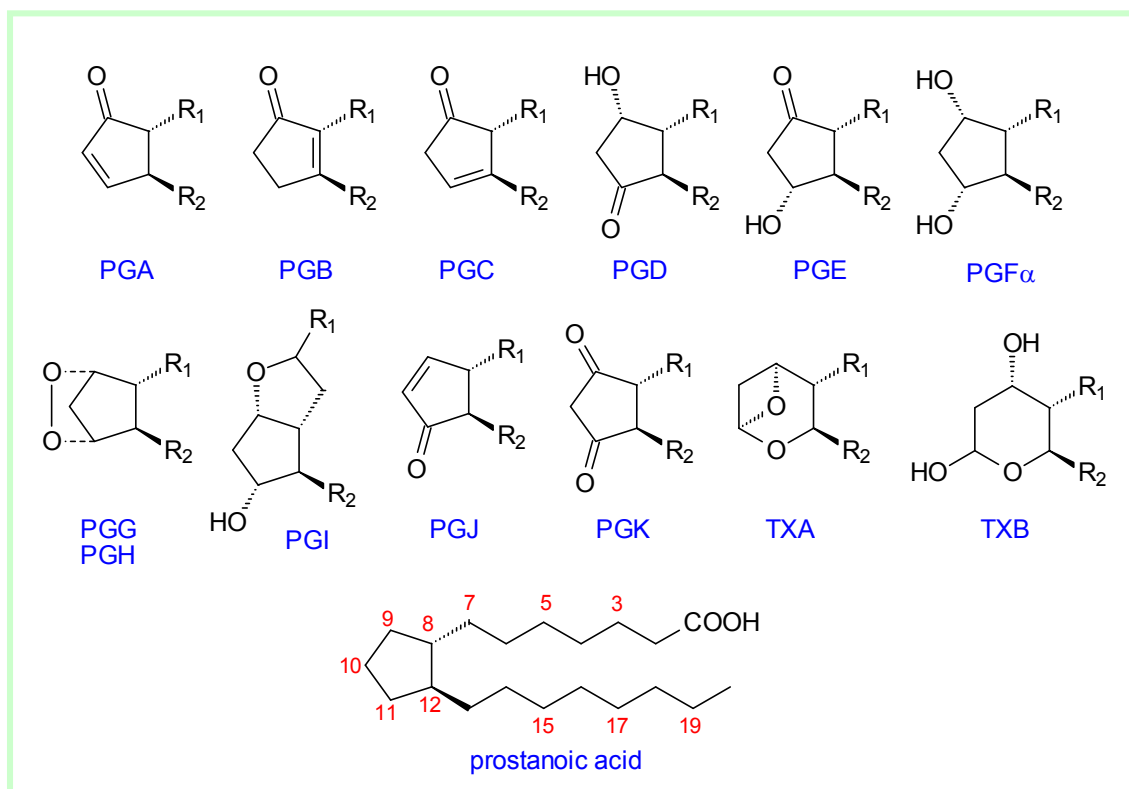


## Chemistry and Biology

### 1. Nomenclature and Structures of Prostanoids

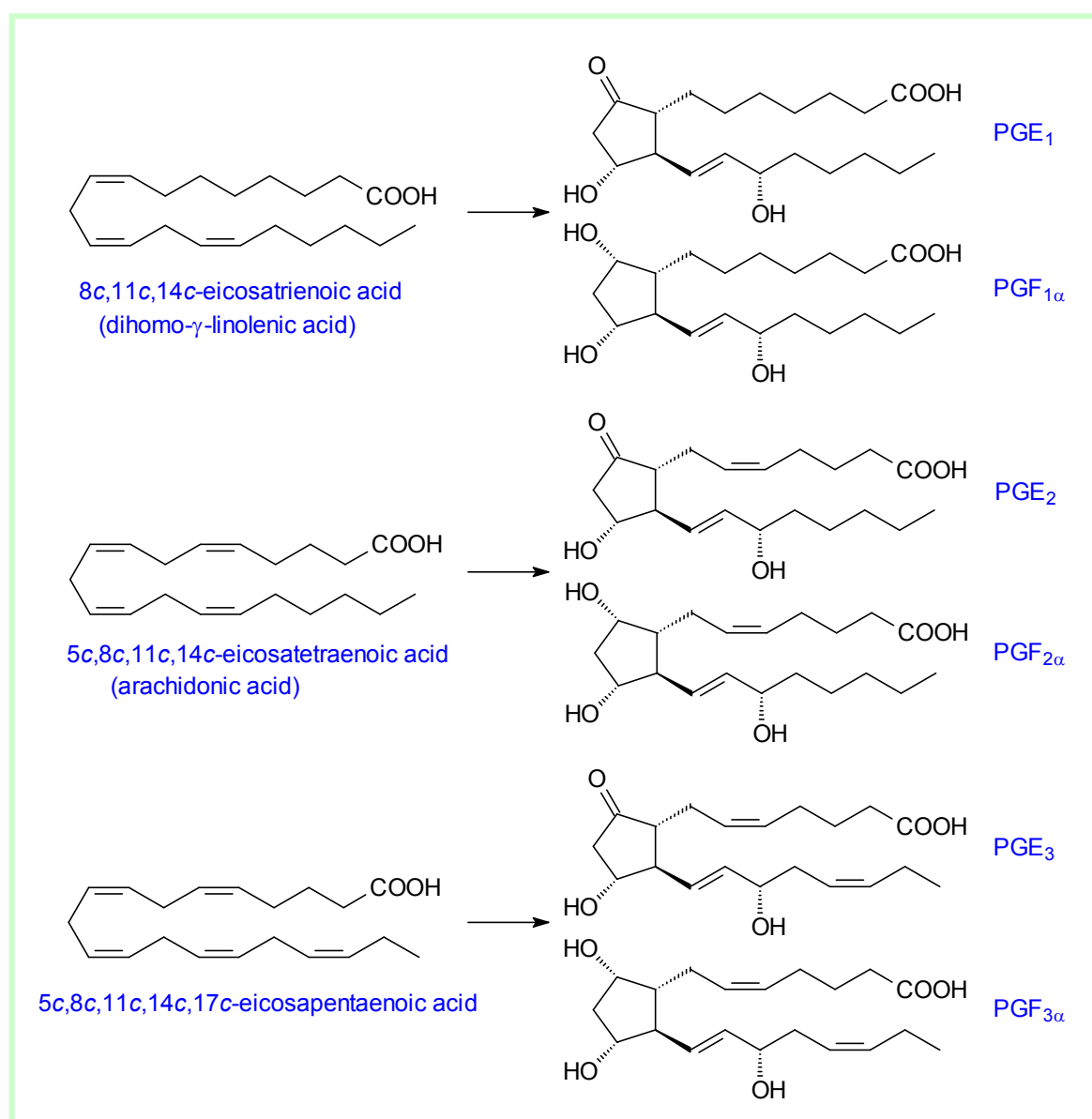
The **prostanoids** are part of a family of biologically active lipids derived from the action of cyclooxygenases or prostaglandin synthases upon the twenty-carbon essential fatty acids or eicosanoids. They can be further subdivided into three main groups, the **prostaglandins**, **prostacyclins** and **thromboxanes**, each of which is involved in some aspect of the inflammatory response. The prostaglandins were first isolated from semen and named from the prostate gland, thought to be their source, as long ago as the 1930s, but it was the 1960s before the biosynthetic relationship to specific essential fatty acids was described when intensive research into their biological properties began. The Nobel Prize for Medicine for 1982 was given to Professors Bengt Samuelsson, John Vane and Sune Bergstrom for their discoveries in this field (see the review by Flower cited below). In general, prostaglandins occur at very low levels in tissues, of the order of nanomolar concentrations, but they have profound biological activities.

In structure, they are best considered as derivatives of a C<sub>20</sub> saturated fatty acid, prostanic acid, which does not itself occur in nature. A key feature is a five-membered ring encompassing carbons 8 to 12, as illustrated below. The thromboxanes are similar but have heterocyclic oxane structures. They are all synthesised by specific enzymes, which confer stereospecificity and chirality on every functional group, and are thus distinct from the **isoprostanes**, which are produced by non-enzymic means.



In the approved nomenclature, each prostaglandin is named using the prefix 'PG' followed by a letter A to K depending on the nature and position of the substituents on the ring. Thus PGA to PGE and PGJ have a keto group in various positions on the ring, and are further distinguished by the presence or absence of double bonds or hydroxyl groups in various positions in the ring. PGF has two hydroxyl groups while PGK has two keto substituents on the ring. PGG and PGH are bicyclic endoperoxides. An oxygen bridge between carbons 6 and 9 distinguishes **prostacyclin (PGI)**. **Thromboxane A (TXA)** contains an unstable bicyclic oxygenated ring structure, while thromboxane B (TXB) has a stable oxane ring. In addition, all prostaglandins have a hydroxyl group on carbon 15 and a *trans*-double bond at carbon 13 of the alkyl substituent ( $R_2$ ).

Further, a numerical subscript (1 to 3) is used to denote the total number of double bonds in the alkyl substituents, and a Greek subscript ( $\alpha$  or  $\beta$ ) is used with prostaglandins of the PGF series to describe the stereochemistry of the hydroxyl group on carbon 9. This is illustrated for prostaglandins PGE and PGF $_{\alpha}$  of the 1, 2 and 3 series below, as examples.

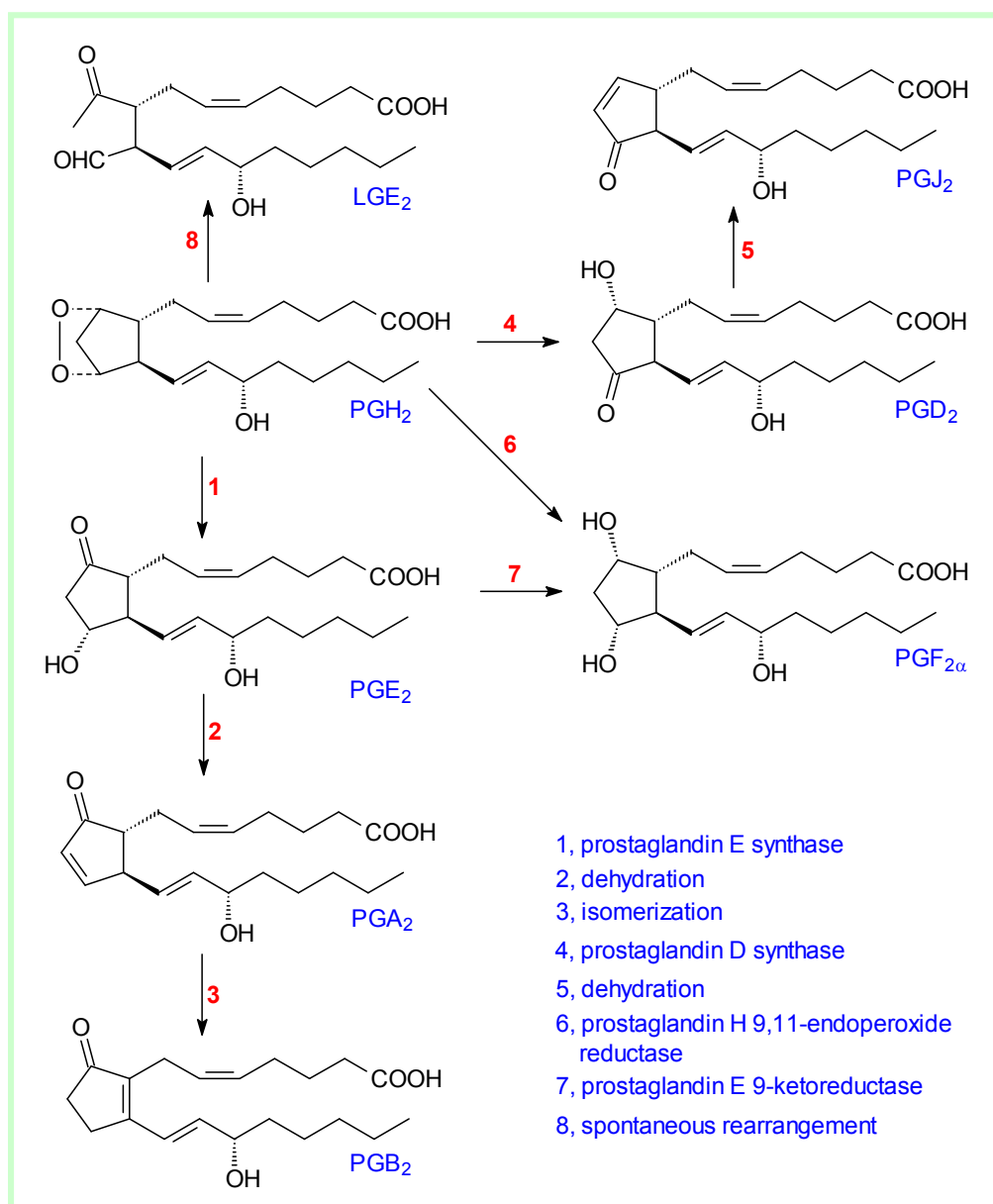


The number of double bonds depends on the nature of the fatty acid precursor. Thus, the prostaglandins PGE<sub>1</sub>, PGE<sub>2</sub> and PGE<sub>3</sub> are derived from 8c,11c,14c-eicosatrienoic (dihomo- $\gamma$ -linolenic), 5c,8c,11c,14c-eicosatetraenoic (arachidonic) and 5c,8c,11c,14c,17c-eicosapentaenoic acids, respectively. Of these, PGE<sub>2</sub> is the most common and is involved in many physiological

processes. Dihomo-prostaglandins derived from arachidonic acid (22:4(n-6)) have recently been detected in cell preparations.

## 2. Biosynthesis of Prostanoids

Eicosanoids, including the prostanoids, are not stored within cells, but are synthesised as required in response to hormonal stimuli. The first step in their synthesis is the release of the substrate fatty acid, such as arachidonic acid, from the cellular phospholipids, by the action of the enzyme phospholipase A<sub>2</sub>, and this is discussed in the **Introductory** document to this series. Next, the free acids are acted upon by one of two related enzymes, cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2) (alternatively termed prostaglandin endoperoxide H synthases-1 and -2 (PGHS-1 and PGHS-2)), as is also discussed in the **Introductory** document. Both enzymes catalyse the same two reactions at different sites, i.e. a cyclooxygenase reaction in which two molecules of oxygen are added to arachidonic acid to form a bicyclic endoperoxide with a further hydroperoxy group in position 15, i.e. to form prostaglandin PGG<sub>2</sub>. The hydroperoxide is then reduced by a functionally coupled peroxidase reaction to form prostaglandin PGH<sub>2</sub>.



PGH<sub>2</sub> is an unstable intermediate from which all other prostanoids are derived by a variety of different enzymic reactions. Some of these are illustrated above (for arachidonate as the primary precursor). The nature and proportions of the various enzymes and of the prostanoids produced differ according to cell type. Indeed different forms of some of the enzymes exist in cells; they may be functionally similar, but differ in amino acid sequence, structure and co-factor requirements. Thus, PGH<sub>2</sub> is converted to PGE<sub>2</sub> by prostaglandin E synthases. At least three distinct forms of this exist, but the main ones are a cytosolic enzyme that operates in conjunction with COX-1, and a membrane-bound enzyme, which is induced by inflammatory stimuli and which functions in concert with the inducible COX-2. PGE<sub>2</sub> is the principal prostanoid found in certain renal cells, for example. Similarly, PGD<sub>2</sub> is formed from PGH<sub>2</sub> by the action of prostaglandin D synthases, which also exist in two forms and are evolutionarily distinct but functionally convergent. One is located in the central nervous system and the other in peripheral tissues.

**Levuglandins**, such as LGE<sub>2</sub>, are formed from PGH<sub>2</sub> by a non-enzymic rearrangement. They have a very short half-life and react rapidly with the free amine groups of proteins and phosphatidylethanolamine (see below).

The most common stereochemical form of PGF<sub>2α</sub> is synthesised by via two main routes. For example, it can be produced directly from PGH<sub>2</sub> by the action of prostaglandin H-endoperoxide reductase, using NADPH. Interestingly, this enzyme can also utilize PGD<sub>2</sub> as a substrate for the synthesis of the second of the four stereochemical forms of PGF<sub>2α</sub>, 9α,11β-PGF<sub>2α</sub>. As an alternative, PGF<sub>2α</sub> is synthesised via PGE<sub>2</sub> by the action of an enzyme prostaglandin E 9-ketoreductase. A of PGF<sub>2α</sub>, is formed from PGD<sub>2</sub> by reduction of the keto group in position 9 by a PGD 11-ketoreductase.

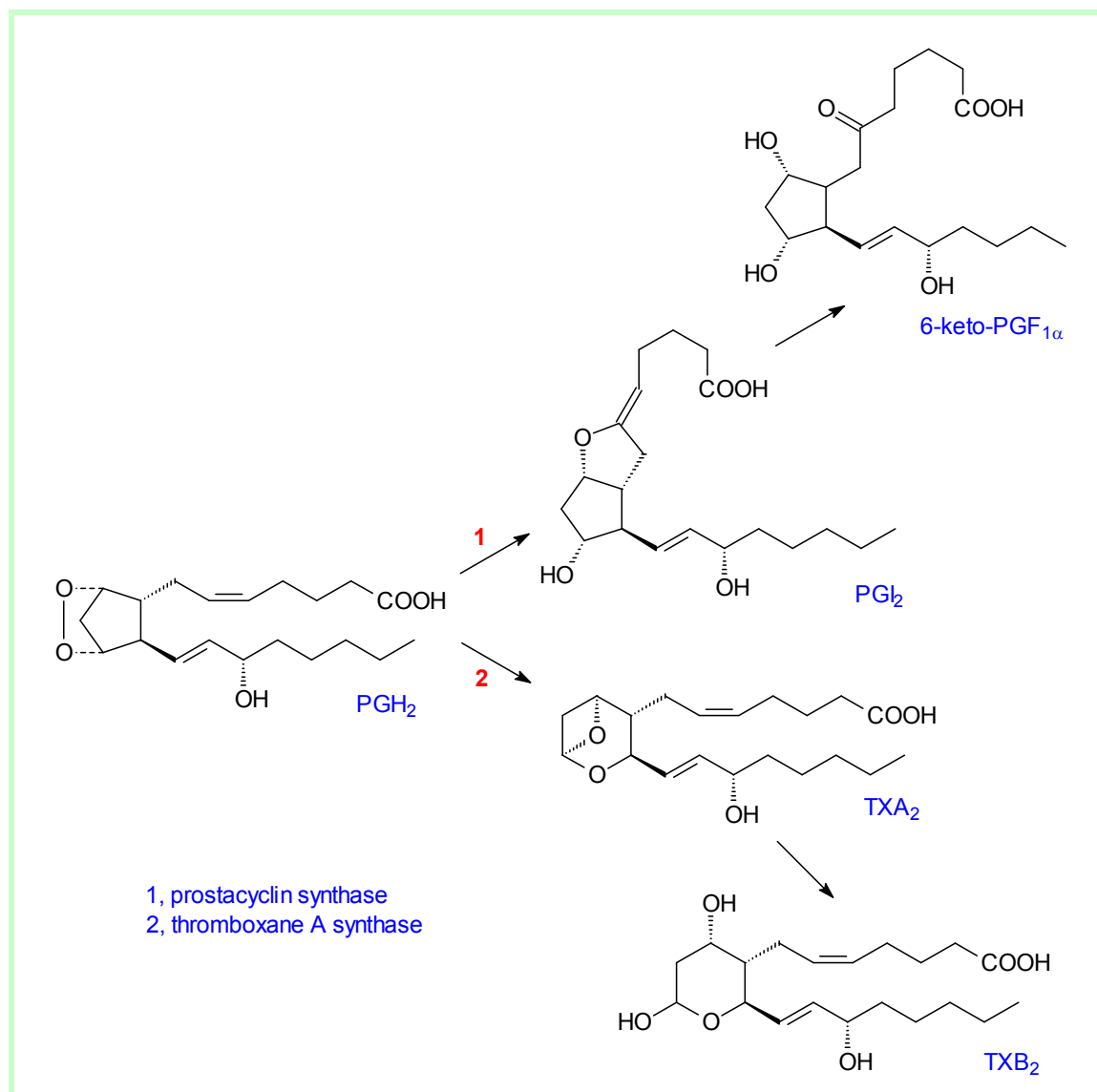
The cyclopentenone prostaglandins A and J, with reactive α,β-unsaturated keto groups and high biological activity, are produced from PGE and PGD, respectively, by spontaneous dehydration reactions, and further modifications can then occur. For example, PGA<sub>2</sub> isomerizes to form the highly unstable PGC<sub>2</sub>, which rapidly undergoes a secondary isomerization to produce PGB<sub>2</sub>. Similarly, PGJ<sub>2</sub> isomerizes to form Δ<sup>12</sup>-PGJ<sub>2</sub> and then promotes a secondary dehydration of the C-15 hydroxyl with 15-deoxy-Δ<sup>12,14</sup>-PGJ<sub>2</sub> as the end product.

**2-Arachidonoylglycerol** and **anandamide** can be substrates for enzymatic conversion to 2-prostanoylglycerols and prostanoylethanolamides (prostamides), respectively, by COX-2 specifically, and thence by further enzymic reactions to PGE<sub>2</sub> and PGF<sub>2α</sub> analogues. While the physiological relevance of this is not yet clear, there is some evidence that 2-PGE<sub>2</sub>-glycerol has biological activity independent of that of the free prostanoid.

Prostacyclin and thromboxanes are also synthesised directly from PGH as illustrated below. Thus, a prostacyclin synthase converts PGH<sub>2</sub> to PGI<sub>2</sub>, while a thromboxane A synthase catalyses the production of TXA<sub>2</sub> from PGH<sub>2</sub>. These enzymes are related to the cytochrome P450 group of proteins and are located on the cytosolic face of the endoplasmic reticulum, so the precursor PGH must cross the membrane. PGI and TXA are the main prostanoids formed in endothelial and smooth muscle cells and in platelets and lung, respectively. Indeed, PGI<sub>2</sub> and some other prostanoids can be produced by cell–cell interactions by using enzymes in adjacent cells, i.e. PGH<sub>2</sub> of platelet origin is converted to PGI<sub>2</sub> in the vascular epithelium or lymphocytes.

The vinyl ether moiety in prostacyclin is unstable below pH 8.0, and PGI<sub>2</sub> is rapidly deactivated non-enzymatically by a hydrolysis reaction to form 6-keto-PGF<sub>1α</sub>. Similarly, TXA<sub>2</sub> contains an unstable ether linkage and is deactivated by non-enzymatic hydrolysis to form inert TXB<sub>2</sub>.

Before they can function, prostanoids that have been newly synthesised must be transported from the cytosol and cross various membranes. This is accomplished by active transporter systems.



Certain pathogenic fungi and yeasts produce 3-hydroxy-eicosanoids from host arachidonic acid and they can hijack the host's COX-2 enzymes to produce 3-hydroxy-prostaglandins from these that are as active biologically as the normal compounds. In addition, the yeast *Candida albicans* and other pathogenic fungi produce PGE<sub>2</sub> *in vitro* from exogenous arachidonate by a novel biochemical mechanism, which does not involve the COX enzymes.

### 3. Prostanoid Catabolism

Prostanoids function close to the site of synthesis, and they are deactivated before they are exported into the circulation as inactive metabolites. Some, such as PGI and TXA, are deactivated spontaneously as described above. However, active enzyme systems also operate, and these function primarily by reaction with the 15(S)-hydroxyl group as discussed in the [Introductory webpage](#). However, a significant portion of the thromboxanes undergoes dehydrogenation at C-11 by an 11-dehydrothromboxane B<sub>2</sub> dehydrogenase to form 11dh-TXB<sub>2</sub>, a metabolite found in human blood plasma and urine.

## 4. The Functions of Prostanoids

Prostaglandins, leukotrienes and thromboxanes are ubiquitous lipids in animal tissues that coordinate a multitude of physiologic and pathologic processes, either within the cells in which they are formed or in closely adjacent cells (they are deactivated too readily to be transported far) in response to specific stimuli. Under normal physiologic conditions, they have essential homeostatic functions in the cytoprotection of gastric mucosa, renal physiology, gestation, and parturition, but they are also implicated in a number of pathological conditions, such as inflammation, cardiovascular disease and cancer.

Prostanoids are sometimes described as local hormones that to act close to the site of their synthesis to coordinate the effects of other hormones in the circulation, although some can undergo facilitated transport from the cell via specific transporters to exert autocrine or paracrine actions. In order to express their activity, they interact with specific G-protein-linked receptors mainly, of which at least nine are known in the mouse and man. Of these receptors, four bind PGE<sub>2</sub> (EP1–EP4), two bind PGD<sub>2</sub> (DP1 and DP2), while others bind specifically to PGF<sub>2α</sub> (FP), PGI<sub>2</sub> (IP) and TXA<sub>2</sub> (TP). The immediate result is an increase or decrease in the rate of generation of cytosolic second messengers (cAMP or Ca<sup>2+</sup>), a change in membrane potential or activation of a specific protein kinase. The different receptors characterized from diverse cell types tend to have high, but not absolute, specificity for particular prostanoids with characteristic functions in each cell. Certain of the cyclopentanone prostanoids (PGA and PGJ series) interact with peroxisome proliferator-activated receptors (PPARs), especially PPAR<sub>γ</sub>, which is a nuclear hormone receptor or ligand-activated transcription factor involved in adipogenesis, glucose homeostasis and lipid metabolism.

The picture of prostanoid actions is complicated by the fact that a given prostanoid can have a number of different biological functions, sometimes opposing, according to the cell type, the nature of the stimulatory response and the type of receptor. For example, PGE<sub>2</sub> can have either pro- or anti-inflammatory effects depending on its interactions with one of four receptors in different cell types. The relative activities of the two iso-enzymes COX-1 and COX-2 are also essential to an understanding of the activity of prostanoids in any given circumstance.

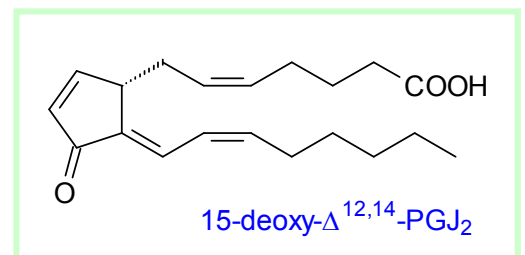
**Inflammation and immune responses:** Arguably the best known of the functions of prostaglandins and thromboxanes in cells is that they modify the inflammatory response, affecting symptoms, such as pain, fever and swelling. In the early days of prostaglandin research, it was evident that prostaglandins injected into tissues could induce all the symptoms of inflammation. However, it is now recognized that the interactions are complex, and prostanoids can act both in a pro- and anti-inflammatory manner according to the nature of the inflammatory stimulus and the specific prostanoid produced, together with the profile of prostanoid receptors in a given type of cell.

Under normal conditions, prostanoid levels in cells are low, but during inflammation both the nature and concentration of prostanoids can change dramatically. For example, macrophages produce both PGE<sub>2</sub> and TXA<sub>2</sub>, but the ratio changes to an excess of PGE<sub>2</sub> with an inflammatory stimulus. In these actions, prostanoids are best viewed as part of complex regulatory networks that modulate the actions of immune cells. PGE<sub>2</sub> in particular has potent pro-inflammatory effects, including inducing fever and enhancing pain, but it also has anti-inflammatory properties, such as suppressing lymphocyte proliferation and inhibiting the production of certain interleukins and other cytokines. It also inhibits the action of 5-lipoxygenase, which is involved in the synthesis of pro-inflammatory leukotrienes, and stimulates the activity of the anti-inflammatory lipoxins. Therefore, PGE<sub>2</sub> has a role in initiating the inflammatory response and in its eventual resolution. There is a particular interest in findings that in its pro-inflammatory role PGE<sub>2</sub> promotes the growth of colorectal tumors (see below). It is also involved in the pathology of rheumatoid arthritis. PGI<sub>2</sub> is also considered to be an important pro-inflammatory prostanoid in relation to pain, especially.

The high levels of prostanoids found in inflammation are presumed to be due to the recruitment of leukocytes and the induction of the COX-2 enzyme (COX-1 appears to have a minor role only), which then produces mainly the pro-inflammatory prostanoids in many tissues. This explains the interest in COX-2 inhibitors for treating arthritis and other chronic inflammatory diseases. Inhibition of cyclooxygenases also explains the role of non-steroidal drugs, such as aspirin, in reducing the symptoms of fever. In the brain, COX-2 is present in neurons and has been implicated in the progression of Alzheimer's disease.

Immune responses are initiated and coordinated by T lymphocytes. Prostanoids are known to interact with T cells in a variety of ways, and appear to modify their development and maturation. Thus, PGE<sub>2</sub> inhibits lymphocyte activation and proliferation, while TXA<sub>2</sub> has opposing effects. Again, the actions of COX-2 (and COX-1) may be the key to triggering antigen-specific inflammation. However, this view may be too simplistic, and there is evidence that COX-2 is pro-inflammatory in the early stages of inflammation, but is beneficial at later stages by generating anti-inflammatory prostanoids. COX-1 derived prostanoids may sustain the inflammatory response.

Although PGD<sub>2</sub> has pro-inflammatory properties in allergic responses, it is also recognized a key anti-inflammatory prostanoid that may be involved in the resolution of inflammation. Similarly, PGJ<sub>2</sub>, Δ<sup>12</sup>-PGJ<sub>2</sub> and the short-lived 15-deoxy-Δ<sup>12,14</sup>-PGJ<sub>2</sub>, the J-series of prostaglandins that were once thought to be simply inactive degradation products of PGD<sub>2</sub>, are now well established as anti-inflammatory regulators, which function via an interaction with PPARγ as discussed briefly above. They may also be involved in the immune response as they are produced in antigen-presenting cells such as activated T lymphocytes. 15-Deoxy-Δ<sup>12,14</sup>-PGJ<sub>2</sub> is important as an inhibitor of tumorigenesis (see below).



Polyunsaturated fatty acids of the *omega*-3 family are known to have anti-inflammatory properties. One explanation is that they inhibit the release of arachidonate from membrane phospholipids for eicosanoid production, or they may compete with arachidonate for the same enzymes of eicosanoid biosynthesis. Another reason may be that the 3-series prostanoids derived from eicosapentaenoic acid (EPA) have different biological activities from those of the 2-series.

**Cardiovascular effects:** Two prostanoids are especially important and have essential but opposing functions in the maintenance of vascular homeostasis, i.e. TXA<sub>2</sub> and PGI<sub>2</sub> (PGE<sub>2</sub> and PGD<sub>2</sub> are also relevant). TXA<sub>2</sub> is synthesised mainly in platelets (which express only COX-1), production being enhanced during platelet activation, and it promotes platelet aggregation, vasoconstriction, and smooth muscle proliferation, even though it has a half-life of only 20-30 seconds. In contrast, prostacyclin is the main product of macro-vascular endothelial cells. It is a potent vasodilator, and it inhibits platelet aggregation and smooth muscle cell proliferation. Thus, it contributes substantially to myocardial protection. COX-2 is the enzyme that provides the main source of prostacyclin. Both TXA<sub>2</sub> and PGI<sub>2</sub> are therefore important mediators of pathological vascular events including thrombosis and atherogenesis, and it is evident that the correct balance between the two prostanoids is essential to good cardiovascular health. The ratio of TxA<sub>2</sub>:PGI<sub>2</sub> seems to be more important than the absolute amounts of these mediators that are produced *in vivo*. Further relevant factors are increased expression and activation of the TP receptor (for TXA<sub>2</sub>) in atherosclerotic lesions, which can directly accelerate atherogenesis and plaque growth.

The cardio-protective effect of aspirin, established by clinical trials, is exerted by the irreversible long-term inhibition of platelet COX-1 and thence of TXA<sub>2</sub> biosynthesis for the lifetime of a platelet in the circulation (aspirin has little effect on PGI synthesis). Indeed, aspirin appears to be the only COX inhibitor with proven cardioprotective activity. In contrast, there is some concern that specific COX-2 inhibitors may have pro-thrombotic effects by inhibiting prostacyclin synthesis relative to

that of thromboxanes. In clinical practice, such potential adverse effects of these drugs have to be balanced against positive effects in other tissues since only 1-2% of patients are believed to be at risk. Once more, polyunsaturated fatty acids of the *omega*-3 family are believed to have beneficial effects.

**Lung:** PGE<sub>2</sub> can have anti-inflammatory and anti-asthmatic effects by activating the EP3 receptor. The role of PGD<sub>2</sub> is more complex, but it may be pro-inflammatory.

**Gastrointestinal system:** COX-1 is always present throughout the human gastrointestinal tract, and produces PGI<sub>2</sub> and PGE<sub>2</sub>, which have protective effects on the gastrointestinal mucosa. Both of these prostanoids reduce acid secretion from parietal cells, while increasing blood flow and stimulating the secretion of mucus. In this instance, the non-steroidal anti-inflammatory drugs, such as aspirin, have negative effects, while the COX-2 inhibitors can be beneficial. On the other hand, these findings are challenged by studies showing that COX-2 is expressed in the intestinal mucosa, and is induced in ulceration, for example, when large amounts of prostaglandins are produced that assist in healing.

**Kidney function:** Prostaglandins generated by both COX-1 and COX-2, especially PGE<sub>2</sub>, assist in the regulation of kidney function by maintaining vascular tone, blood flow, and salt and water excretion. PGE<sub>2</sub> is required for the regulation of sodium re-absorption, while PGI<sub>2</sub> (and possibly PGE<sub>2</sub>) increases potassium secretion. In addition, this PGI<sub>2</sub> with its well-known vasodilatory properties increases renal blood flow and the flow of fluids through the kidney. These actions are mediated via specific receptors, four of which have been identified for PGE<sub>2</sub>, for example.

**Reproductive system:** Prostaglandins produced both by COX-1 and COX-2 are involved in many aspects of the reproduction, from ovulation and fertilization through to labour. They are produced in the fetus and in the placenta as well as in other reproductive tissues. In particular, the synthesis of PGE<sub>2</sub> and PGF<sub>2α</sub> is increased appreciably during labour, and these prostaglandins are in fact used as drugs to induce labour.

**Cancer:** COX-2 is over-expressed in many cancers, including those of the breast, colon and prostate. In particular, PGE<sub>2</sub> produced by the enzyme occurs at much higher concentrations in tumor than in normal tissues. It promotes survival of tumor cells by inhibiting apoptosis and inducing proliferation, and by increasing cell motility and migration. In addition, via its effect on the immune system and inflammation, it has adverse effects in relation to the destruction of tumors. In consequence both the non-steroidal anti-inflammatory drugs, such as aspirin, and the COX-2 inhibitors have been found to have beneficial effects towards some types of cancer. Thromboxane TXA<sub>4</sub> may also be a pro-carcinogenic mediator.

15-Deoxy-Δ<sup>12,14</sup>-PGJ<sub>2</sub> (15-d-PGJ<sub>2</sub>), a potent anti-inflammatory regulator that functions via an interaction with PPAR<sub>γ</sub>, also regulates adipogenesis and tumorigenesis and is produced by a variety of cells. An active transport system may carry it to the cells where it is required, and thence it is transported into the nucleus, where it affects gene transcription. Unlike PGE<sub>2</sub>, 15-d-PGJ<sub>2</sub> is a potent anti-tumor agent, inhibiting tumor growth both *in vitro* and *in vivo* in many tissues. It appears to act in a number of ways, for example directly by inhibiting proliferation and stimulating apoptosis. Also, it can interact indirectly to inhibit migration of tumor cells, and it can affect surrounding cells to reduce the expression of key receptors. However, some experimental conditions have been identified in which it exerts contrary effects.

In general, PGE<sub>2</sub> and 15-d-PGJ<sub>2</sub> have profound but opposing effects on tumorigenesis. It is evident that the prostaglandin synthases that are responsible for their biosynthesis are likely to be key targets for the development of anticancer drugs.

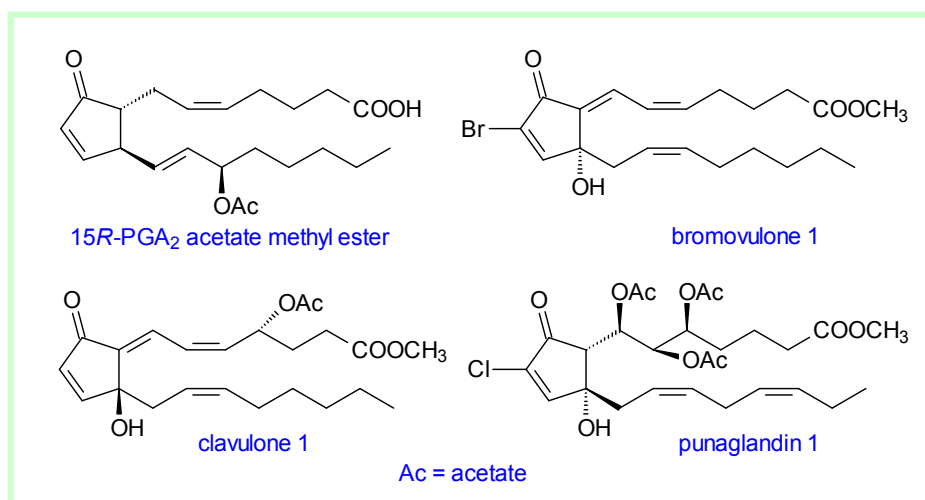
**Protein metabolism:**  $\gamma$ -Keto aldehydes such as the levuglandins and isolevuglandins, the latter produced in an analogous manner to the isoprostanes, have a remarkable reactivity towards proteins, forming adducts with greatly modified biological functions. Thus, these di-aldehydes react with lysyl residues on proteins to form first Schiff base adducts and thence pyrrole derivatives, which are able to form intra- and intermolecular protein-protein cross-links. Protein adducts of this type are not at all easy to analyse, but those in brain have been correlated with the severity of Alzheimer's disease, for example. Indeed, levuglandins and isolevuglandins are believed to be among the most potent neurotoxic products of lipid oxidation.

Levuglandins also react with **phosphatidylethanolamine** to form hydroxy-lactam derivatives, which may be better markers of oxidative injury from a practical standpoint as they are more easily analysed.

**Parasitic infections:** It has been established that a number of parasitic organisms produce prostaglandins in the same way as their mammalian hosts, and by similar enzymic mechanisms. They may play a part in the pathogenesis of parasitic diseases.

## 5. Some Exotic Prostanoids

Marine invertebrates, including sponges, corals, and molluscs, contain a wide range of prostaglandins, many of which are of the conventional type such as PGE<sub>2</sub>, PGF<sub>2</sub> and so forth. They are presumed to perform similar functions as in mammals, and are also involved in the regulation of oogenesis and spermatogenesis, ion transport and defense. One species of coral (*Plexaura homomalla*) contains up to 8% of its dry mass as PG esters, and for many years this was a primary source of material for experimental work. In many marine invertebrates, the prostaglandins exist largely in esterified form rather than the free state.



In addition, a number of novel prostanoids have been discovered, some of which are illustrated above, which differ in stereochemistry from the typical prostanoids, or contain acetyl groups, or are substituted with halogen atoms, such as chlorine or bromine. Little is known of the biochemistry or function of the clavulones, bromovulones or punaglandins in marine organisms, but there is increasing interest in them because of reported anti-tumor activities.

## 6. Prostanoid Analysis

Analysis of prostanoids is not a simple task, because they occur at such low levels in tissues and because of their high reactivity. Extraction must be carried out under mild conditions as rapidly as

possible, and solid-phase extraction methods are now available that set the standard. Subsequent analysis usually involves derivatization to improve volatility, followed by analysis by gas chromatography linked to mass spectrometry. Immunoassays are available that may be suitable for some clinical applications, but they are not sensitive to minor differences in prostanoid structure.

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Last updated: Dec. 14<sup>th</sup>, 2009

