Prostaglandins and Leukotrienes

BCH 560
2nd Semester 1427
Prostaglandins

• Prostaglandins are a family of chemical messengers which are involved in local signaling within tissues.

• The effects of the signal are highly dependent upon both the specific type of prostaglandin as well as the properties of the target tissue cells. For instance, the same prostaglandin may have different effects when acting upon the endothelial cells of the gastrointestinal tract than on the vasculature of inflamed tissue.
PGs

• PGs and their metabolites are widely distributed in the body.

• Belong to a class of substances called eicosanoids.

• Eicosanoids are a group of substances derived from fatty acids and include:
  – prostaglandins,
  – thromboxanes, and
  – leukotrienes,

• Formed from precursor poly unsaturated fatty acids by the incorporation of oxygen atoms into the fatty acid chains. This reaction is catalysed by cyclo-oxygenases.
• The prostaglandins together with the thromboxanes form the **prostanoid** class of fatty acid derivatives;
• the prostanoid class is a subclass of **eicosanoids**.
History and name

• The name *prostaglandin* derives from the prostate gland.

• When prostaglandin was first isolated from seminal fluid in 1936, it was believed to be part of the prostatic secretions.

• Prostaglandins are produced by the seminal vesicles.

• In 1971, it was determined that aspirin-like drugs could inhibit the synthesis of prostaglandins.

• The biochemists Sune K. Bergström, Bengt I. Samuelsson and John R. Vane jointly received the 1982 Nobel Prize in Physiology or Medicine for their research on prostaglandins.
• Every prostaglandin contains **20 carbon atoms**, including a **5-carbon ring**.

• They are **mediators** and have a variety of **strong physiological effects**;

• Although they are technically hormones, they are rarely classified as such-known as **local hormones**, as they are secreted in the same tissue in which they act

• Play important functions in the animal body.

• Prostaglandins are divided into 10 series, Named from A-H and F has alpha and beta depending on the spatial configuration of the carbon 9 OH group These different PGs differ in the structure of the characteristic 5-membered ring.
May be $\alpha$ or $\beta$

PGE1
PGD$_2$
PGF$_{2\alpha}$
PGE$_2$
Arachidonic Acid

\[ \text{CH}_3(\text{CH}_2)_4(\text{CH}=-\text{CHCH}_2)_4\text{CH}_2\text{CH}_2\text{C}=\text{OH} \]

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2\text{CH}_2\text{C}=\text{OH} \]

5,8,11,14-icosatetraenoic acid or arachidonic acid
Types of PGs

- PGs are divided into three main types:
  - 1 and 2, which are produced by omega 6 fatty acids; and
  - 3, which is produced by omega 3 fatty acids.
  - The precursors for each are: 1, GLA; 2, AA; and 3 is Eicosapentaenoic acid (EPA.)

- Prostaglandins 1 and 3 are considered to be beneficial, and function to dilate blood vessels, reduce clotting, lower LDL and cholesterol levels, raise beneficial HDL and have anti-inflammatory actions. Prostaglandins 2 are considered harmful and act in direct opposition to prostaglandins 1 and 3, they signal lymphocytes to become more active and thus increase the immune response that is already operating outside of normal controls in the rheumatoid patient]
Fatty Acids

The Omega-6 Family
Linoleic Acid (LA)
(Found in vegetable oils, seeds and nuts.)

Body converts LA into:

Gamma-Linolenic Acid (GLA)
(GLA is also found in borage and primrose oil.)

Body converts GLA into:

Arachidonic Acid (AA)
(AA is also found in meat.)

The Omega-6 Family of Prostaglandins

The Omega-3 Family
Alpha-Linolenic Acid (LNA)
(Found in green leafy vegetables, flax, flaxseed oil, canola oil, walnuts, and Brazil nuts.)

Body converts LNA into:

Eicosapentaenoic Acid (EPA)
(EPA is also found in fish oil.)

Body converts EPA into:

Docosahexaenoic Acid (DHA)
(DHA is also found in fish oil.)

The Omega-3 Family of Prostaglandins
Letters A to H, depending on the substituents on the cyclopentane:

<table>
<thead>
<tr>
<th></th>
<th>PGA</th>
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<tbody>
<tr>
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<td><img src="image9" alt="Structure" /></td>
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<tr>
<td>PGD</td>
<td>PGE (ether)</td>
<td>PGF (phosphate)</td>
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</table>
May be $\alpha$ or $\beta$

- **PGE1**
- **PGF$_{2\alpha}$**
- **PGD$_2$**
- **PGE$_2$**
Location

• Prostaglandins are found in virtually all tissues and organs.
• These are autocrine and paracrine lipid mediators that act upon
  – platelet,
  – endothelium,
  – uterine and
  – mast cells,
  – among others.
Source of PGs

• They are synthesized in the cell from the essential fatty acids (EFAs):
  – Gamma-linolenic acid (GLA, an ω-6 EFA, via DGLA) - yielding the series-1 prostaglandins
  – Arachidonic acid (AA, ω-6) - yielding series-2
  – Eicosapentaenoic acid (EPA, ω-3) - yielding series-3
Biosynthetic Pathways

• An intermediate is created by phospholipase-A2, then passed into one of either the cyclooxygenase pathway or the lipoxygenase pathway to form either prostaglandin and thromboxane or leukotriene.

• The cyclooxygenase pathway produces
  – thromboxane,
  – prostacyclin and
  – prostaglandin D, E and F.

• The lipoxygenase pathway is active in leukocytes and in macrophages and synthesises
  – leukotrienes.

• The cytochrome P-450 pathway

• Prostaglandins are released through the prostaglandin transporter on the cell's plasma membrane.
Prostaglandins and Thromboxanes

Membrane phospholipids

Phospholipase

Arachidonic acid (AA)

Microsomal cytochrome P450 monooxygenases

- 5-Lipoxygenase
  - Leukotrienes (LT)
- Cyclooxygenase
  - PGH₂
    - Prostaglandins (PG)
    - Thromboxanes (Tx)

PGs
Schematic summary of the biosynthetic pathway for eicosanoids derived from arachidonic acid.
Biosynthesis

Diacylglycerol or phospholipid

Phospholipase C \rightarrow \text{Phospholipase A}_2 \rightarrow \text{Arachidonic acid}

\text{HPETE (hydroperoxy-eicosatetraenoic acid)}

\text{Lipoxygenase (FLAP, Alox5)}

\text{PGH}_2 \text{ synthase (cox-1 or -2 and peroxidase)}

\text{PGD synthase}

\text{PGD}_2 \rightarrow \text{PGE synthase}

\text{PGE}_2 \rightarrow \text{Prostacyclin synthase}

\text{Prostaglandin H}_2 \text{ (PGH}_2\text{)} \rightarrow \text{Thromboxane synthase}

\text{6-keto-PGF}_{1\alpha} \rightarrow \text{Prostacyclin (PGI}_2\text{)} \rightarrow \text{Thromboxane (TXA}_2\text{)} \rightarrow \text{Thromboxane (TXA}_2\text{)}

\text{H}_2\text{O}

\text{Leukotriene A}_4 \rightarrow \text{Glutathione-S-transferase}

\text{Leukotriene C}_4 \rightarrow \text{Leukotriene D}_4 \rightarrow \text{Leukotriene E}_4

\text{Glutathione}

\text{Glutamic acid}

\text{Endothelium}

\text{Platelets}
FIG. 2. Cyclooxygenase and lipoxygenase pathways. The nomenclature of enzymes is as follows: 1, phospholipases; 2, PG endoperoxide synthase (cyclooxygenase); 3, PG endoperoxide synthase (hydroperoxidase); 4, PG synthase (PGH-1 isomerase); 5, PG synthase (PGH-2 isomerase); 6, PG synthase (PGH-1 isomerase); 7, PG synthase (PGH-2 isomerase); 8, TX synthase; 9, LTB synthase; 10, LTA synthase; 11, LTA synthase; 12, LTB synthase; 13, LTA synthase; 14, y-glycylglycine; 15, dipeptidase. The broken lines indicate the nonenzymatic processes. The properties of these enzymes are described by Shimizu et al. (1977a), Shimizu et al. (1982), and Yamao et al. (1983, 1986). 5-HETE, 5-hydroxyethyl-5-etheno-2,10,14,16,18-eicosapentaenoic acid; PG endoperoxide synthase, PGE synthase.
PROSTAGLANDINS

OMEGA 6 (Linoleic acid) → GAMMA-LINOLENIC ACID (GLA) → DIHOMO-GAMMA-LINOLENIC ACID (DGLA) → ARACHIDONIC ACID (AA)

SERIES 1
- prevents blood platelet aggregation
- removes sodium excess fluid via the kidneys
- relaxes blood vessels, lowers blood pressure
- decreases inflammation (arthritis)
- improves insulin function (diabetics)
- regulates calcium metabolism
- improves functioning of T-cells (improved immunity)
- prevents release of AA

.Series 2
"The Bad Prostaglandins"
These have the opposite effect of Series 1 Prostaglandins

OMEGA 3 (alpha linolenic acid) → STEARIDONIC ACID (SDA) → EICOSATETRAENOIC ACID (ETA) → EICOSAPENTAENOIC ACID (EPA)

SERIES 3
Very powerful in preventing the release of arachidonic acid
Cyclooxygenases

- Prostaglandins are produced following the sequential oxidation of AA, DGLA or EPA by cyclooxygenases (COX-1 and COX-2) and terminal prostaglandin synthases.
- The COX-1 is responsible for the baseline levels of prostaglandins, whereas COX-2 produces prostaglandins through stimulation.
- However, while COX-1 and COX-2 are both located in the blood vessels, stomach and the kidneys, prostaglandin levels are increased by COX-2 during inflammation.
Prostaglandin E synthase

• Prostaglandin E2 (PGE2) is generated from the action of prostaglandin E synthases on prostaglandin H2 (PGH2).
• Several prostaglandin E synthases have been identified.
• To date, microsomal prostaglandin E synthase-1 emerges as a key enzyme in the formation of PGE2
Other terminal prostaglandin synthases

- Terminal prostaglandin synthases have been identified that are responsible for the formation of other prostaglandins.
- For example, hematopoietic and lipocailin prostaglandin D synthases (hPGDS and IPGDS) are responsible for the formation of PGD2 from PGH2.
- Similarly, prostacyclin (PGI2) synthase (PGIS) converts PGH2 into PGI2.
- A thromboxane synthase (TxAS) has also been identified.
- Prostaglandin F synthase (PGFS) catalyzes the formation of $9\alpha,11\beta$-PGF2$\alpha,\beta$ from PGD2 and PGF2$\alpha$ from PGH2 in the presence of NADPH.
- This enzyme has recently been crystallized in complex with PGD2 and bimatoprost (a synthetic analogue of PGF2$\alpha$).
Functions of PGs

- Prostaglandins have a wide variety of actions, including, for example muscular constriction and mediate inflammation. Other effects include calcium movement, hormone regulation and cell growth control.
- Thromboxane is synthesised in platelets and causes vascular constriction and platelet aggregation.
- Prostacyclin comes from cells in the blood vessel walls and is antagonistic to thromboxane.
- Prostaglandins are potent but have a short half-life before being inactivated and excreted. Therefore, they exert only a paracrine (locally active) or autocrine (acting on the same cell from which it is synthesized) function.
• Prostaglandins act as **local chemical messengers**. Unlike hormones, which circulate in blood and act on distant organs, prostaglandins signal from cell to cell but over short ranges.

• Apart from **PGE and PGF** types, many prostaglandins are very short lived, with half lives as short as 30 seconds for thromboxane.

• Many functions are associated with control over contraction of **smooth muscle** or the intracellular non-muscle actomyosin system.

• For PGE and PGI, actions appear to be mediated through activation of **adenylate cyclase** and elevated intracellular levels of cyclic AMP. PGF and TXA seem to oppose the increase in cyclic AMP.
• **Activation of the inflammatory response**, production of pain, and fever. When tissues are damaged, white blood cells flood to the site to try to minimize tissue destruction. Prostaglandins are produced as a result.

• **Blood clots formation when a blood vessel is damaged.** A type of prostaglandin called thromboxane stimulates constriction and clotting of platelets. Conversely, PGI2, is produced to have the opposite effect on the walls of blood vessels where clots should not be forming.

• **Certain prostaglandins are involved with the induction of labor and other reproductive processes.** PGE2 causes uterine contractions and has been used to induce labor.

• **Prostaglandins are involved in several other organs such as the gastrointestinal tract** (inhibit acid synthesis and increase secretion of protective mucus), **increase blood flow in kidneys**, and **leukotriens promote constriction of bronchi associated with asthma**.
Prostaglandins play a role in the following reproductive functions:

1) conception;
2) luteolysis;
3) menstruation; and
4) parturition.

It has also been proposed that Prostaglandin A may be the natriuretic hormone, the circulating hormone which controls sodium reabsorption by the kidney.

Prostaglandins are also implicated:

1) in the fluid transfer in the gut;
2) as causative agents of diarrhea that accompanies medullary carcinoma of the thyroid or neural crest tumors;
3) in reducing blood pressure in humans with essential hypertension;
4) in fatty acid metabolism, including lipolysis; and
5) as mediators of the inflammatory response.
• **PGE1** prevents blood platelets from sticking together, thereby helping to prevent heart attacks and strokes which are caused by blood clots.

• **PGE1** relaxes blood vessels, improving circulation and lowering blood pressure. It reduces inflammation, makes insulin work more effectively and enhances the T-cell function of the immune system.

• **PGE2** promotes platelet aggregation, the first step to clot formation, increasing the risk for heart attack and stroke. It makes the kidneys retain sodium, leading to water retention, and it causes inflammation. Diets high in saturated fats (arachidonic acid) increase levels of this pro-inflammatory prostaglandin.

• **PGE3** has similar functions as prostaglandin E1. It also has a powerful effect of preventing the release of arachidonic acid stored in cell membranes and its conversion to prostaglandin E2.
• **PGE2** stimulates:
  • vascular dilation
  • Bronchio-dilation
  • gastrointestinal and
  • uterine-contraction
  • **inflammatory response**
    – Mimics hormones that act through cyclic AMP
    – Inhibits platelet aggregation

• **PGF2** stimulates:
  • vascular constriction
  • Bronchio-constriction
  • **smooth muscle contraction**, e.g. intestinal tract, uterus intrauterine injection induces expulsion of uterine contents breakdown of corpus luteum

• **PGI2** inhibits
  – **platelet aggregation** (increases cAMP)
  – **vascular constriction**
  – Bronchio-constriction
  – gastrointestinal and uterine contraction

• **TXA2** stimulates
  – **platelet aggregation** (decreases cAMP)
  – **vascular constriction**
  – Bronchio-constriction
• In particular, PGI2 and TXA2 appear to act as a mutually opposed pair.
• TXA2 is produced by platelets, and stimulates their activation, a **positive feedback** loop that gives a rapid thrombotic response when triggered.
• TXA2 action is **kept in check by PGI2** secreted by vascular epithelium.
• If vascular epithelium is intact, PGI prevents clotting, but on vascular damage, loss of PGI synthesis shifts the balance in favour of TXA, and platelet aggregation occurs.
Some prostaglandins may participate in memory and other brain functions.

Some prostaglandins sensitize nerve endings that transmit pain signals to the spinal cord and brain.

Two prostaglandins relax muscles in the lungs; another contracts them.

Two prostaglandins increase blood flow in the kidney.

Two prostaglandins protect the lining of the stomach.

Two prostaglandins contract uterine muscles; another relaxes them.

Some prostaglandins dilate small blood vessels, which leads to the redness and feeling of heat associated with inflammation.
<table>
<thead>
<tr>
<th>Prostaglandin</th>
<th>Physiological Function(s)</th>
</tr>
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<tbody>
<tr>
<td>Thromboxane $A_2$ (TXA$_2$)</td>
<td>Platelet Aggregation (blood clot formation) &amp; Vasoconstriction</td>
</tr>
<tr>
<td>Prostacyclin (PGI$_2$)</td>
<td>Anti-aggregation (blood thinning) &amp; Vasodilation</td>
</tr>
<tr>
<td>PGE$_2$</td>
<td>Induce immune response, Vasodilation, Protect gastric mucosa</td>
</tr>
</tbody>
</table>
Some examples of Prostaglandins and their application

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinoprost Tromethamine PGF2a</td>
<td><img src="image1" alt="Structure" /></td>
<td>Use to induce abortion</td>
</tr>
<tr>
<td>Prostin F2a</td>
<td></td>
<td>Salt given by intraamniotic administration</td>
</tr>
<tr>
<td>Dinoprostone PGE2 prostin E2</td>
<td><img src="image2" alt="Structure" /></td>
<td>Use to induce abortion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administered as a vaginal suppository.</td>
</tr>
<tr>
<td>Carboprost Tromethamine PGF2a (S)-Methyl-PGF2a</td>
<td><img src="image3" alt="Structure" /></td>
<td>Use to induce abortion or to ameliorate severe postpartum hemorrhage</td>
</tr>
<tr>
<td>Alprostadil PGE1 prostin VR Pediatric</td>
<td><img src="image4" alt="Structure" /></td>
<td>For use in neonates with patent ductus until surgery can be performed to correct this congenital defect.</td>
</tr>
<tr>
<td>Misoprostol (R,S)-Methyl-16-Hydroxy-PGE1, Methyl ester (Cytotec)</td>
<td><img src="image5" alt="Structure" /></td>
<td>Gastric antisecretory and gastroprotective effects</td>
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</table>
PG Receptors

- There are currently nine known receptors of prostaglandins on various cell types.
- Prostaglandins ligate a subfamily of cell surface seven-transmembrane receptors, G-protein-coupled receptors.
- These receptors are termed DP1-2, EP1-4, FP, IP, and TP, corresponding to the receptor that ligates the corresponding prostaglandin (e.g., DP1-2 receptors bind to PGD2).
- Prostaglandins thus act on a variety of cells such as vascular smooth muscle cells causing constriction or dilation, on platelets causing aggregation or disaggregation and on spinal neurons causing pain.
• Prostaglandins possess diverse biologic activities and are therefore significant in the pathophysiology of a wide array of diseases.

• The tissue-specific and non-overlapping properties of prostaglandins reflect the compartmentalized nature of receptors through which they act. Many prostaglandin receptors are G-protein coupled receptors, designated EP, FP, IP, TP, and DP; their cognate ligands are PGE2, PGF2α, PGI2, TXA2, and PGD2, respectively.

• In light of the many activities of PGE2, it is not surprising that 4 distinct receptor subtypes (EP1-4) have been found to transmit signals from this molecule.

• All 9 prostaglandin receptors have been cloned and their physiologic roles explored in receptor knock-out mice.

• Although there is obvious therapeutic potential in the ability to block specific activities of prostaglandins, the physiologic role of the receptors is only partially characterized, and subtype-selective antagonists remain elusive.
Role in pharmacology

- NSAIDs inhibit cyclooxygenase and reduce prostaglandin synthesis.
- Corticosteroids inhibit phospholipase A2 production by boosting production of lipocortin, an inhibitor protein.
- Relatively new drugs, known as COX-2 selective inhibitors or coxibs, are used as specific inhibitors of COX-2 (Coxibs).
- The development of these drugs allowed the circumvention of the negative gastrointestinal effects while effectively reducing inflammation.
- However, recently, it has been shown that both NSAIDs and Coxibs can raise the risk of myocardial infarction, when taken on a chronic basis for at least 18 months.
- One emerging hypothesis that may explain the cardiovascular effects is that coxibs create an imbalance in circulating TxA2 and PGI2 levels. An increased in the ratio of TxA2/PGI2 could lead to increased platelet aggregation and dysregulation of platelet homeostasis.
Uses of synthetic prostaglandins

• To induce childbirth, parturition or abortion (PGE2 or PGF2, with mifepristone);
• To prevent closure of ductus arteriosus in newborns with particular cyanotic heart defects
• To prevent and treat peptic ulcers (PGE)
• As a vasodilator in severe Raynaud's phenomenon or ischemia of a limb
• In pulmonary hypertension
• In treatment of glaucoma (as in bimatoprost ophthalmic solution, a synthetic prostamide analog with ocular hypotensive activity)
• To treat erectile dysfunction or in penile rehabilitation following surgery (PGE1 as alprostadil).
Effects of Aspirin and other Pain Killers

• Prostaglandins induce inflammation, pain, and fever. Aspirin blocks cyclooxygenase, COX-1 and COX-2, involved with the ring closure and addition of oxygen to arachidonic acid converting to prostaglandins. The acetyl group on aspirin is hydrolyzed and then bonded to the alcohol group of serine as an ester. This has the effect of blocking the channel in the enzyme and arachidonic can not enter the active site of the enzyme.

• By inhibiting or blocking this enzyme, the synthesis of prostaglandins is blocked, which in turn relieves some of the effects of pain and fever.

• Aspirin is also thought to inhibit the prostaglandin synthesis involved with unwanted blood clotting in coronary heart disease. At the same time an injury while taking aspirin may cause more extensive bleeding.
Non-steroidal anti-inflammatory drugs (NSAIDS)

- NSAIDs including acetylsalicylate (Aspirin), acetaminophen (Tylenol) and ibuprofen are inhibitors of prostaglandin synthase.
- The effect on the PGI/TXA pair results in an anti-thrombotic effect, protective against stroke and heart attack (but promoting a risk from bleeding ulcers).
- Vasodilation reduces headache.
- Inhibition of PGE reduces inflammation.